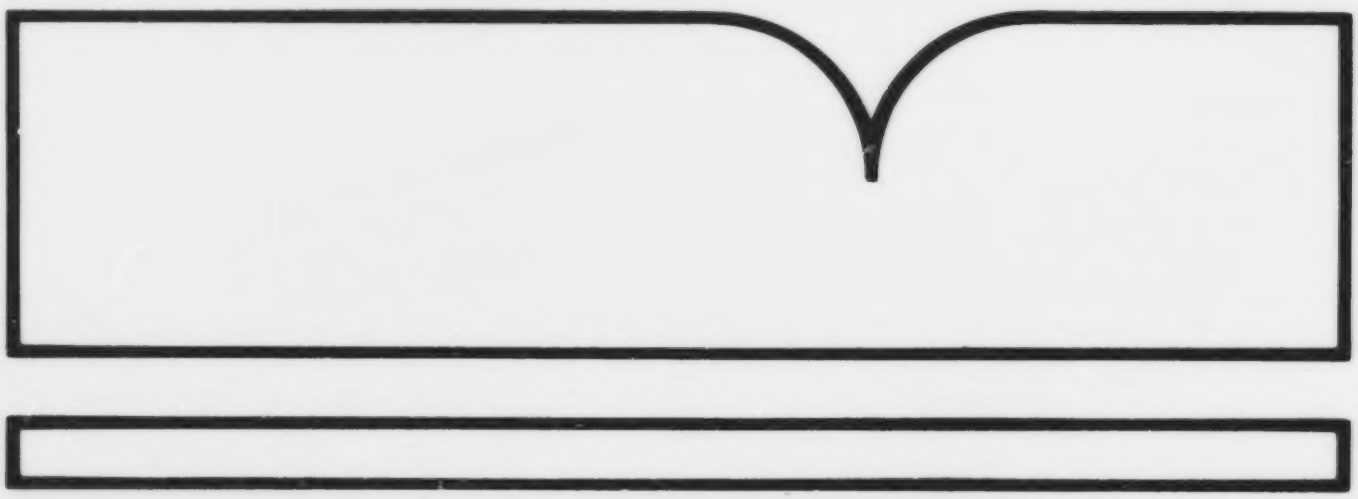
PB88-174511

Health and Environmental Effects Profile for Lead Alkyls

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jul 85



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/X-85/285		PB88-174511

4. TITLE AND SUBTITLE	5. REPORT DATE
Health and Environmental Effects Profile for Lead Alkyls	July 1985
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The Health and Environmental Effects Profile for lead alkyls was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Lead alkyls have been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for lead alkyls is 0.0084 µg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for lead alkyls is 10.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	97
	20. SECURITY CLASS (This page)	22. PRICE
	Unclassified	A05 14.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-174511

EPA/600/X-85/285
July 1985

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR LEAD ALKYLS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	1
1.4.	USE DATA	8
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	9
2.1.	WATER	9
2.1.1.	Hydrolysis and Chemical Degradation	9
2.1.2.	Photolysis	10
2.1.3.	Microbial Degradation	10
2.1.4.	Transport	11
2.2.	AIR	12
2.2.1.	Chemical Removal	12
2.2.2.	Physical Removal	14
2.3.	SOIL	15
2.4.	SUMMARY	16
3.	EXPOSURE	18
3.1.	WATER	18
3.2.	FOOD	19
3.3.	INHALATION	19
3.4.	DERMAL	20
4.	PHARMACOKINETICS	21
4.1.	ABSORPTION	21
4.2.	DISTRIBUTION	22
4.3.	METABOLISM	24
4.4.	EXCRETION	25
5.	EFFECTS	27
5.1.	CARCINOGENICITY	27
5.2.	MUTAGENICITY	28
5.3.	TERATOGENICITY	29
5.4.	OTHER REPRODUCTIVE EFFECTS	31
5.5.	CHRONIC TOXICITY	32
5.6.	OTHER RELEVANT INFORMATION	35

TABLE OF CONTENTS (cont.)

		Page
6.	AQUATIC TOXICITY	40
6.1.	ACUTE EFFECTS	40
6.2.	CHRONIC EFFECTS	42
6.3.	PLANT EFFECTS	42
6.4.	RESIDUES	43
6.5.	OTHER RELEVANT INFORMATION	44
7.	EXISTING GUIDELINES AND STANDARDS	45
7.1.	HUMAN	45
7.2.	AQUATIC	45
8.	RISK ASSESSMENT	46
9.	REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	53
9.1.	REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY	53
9.2.	WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY	65
10.	REFERENCES	68
APPENDIX:	LITERATURE SEARCHED	86

LIST OF TABLES

No.	Title	Page
1-1	Lead Alkyl CAS Numbers, Molecular Weights, Empirical Formulas and Structures.	2
1-2	Physical and Chemical Properties for Tetraethyl and Tetramethyl Lead	3
1-3	United States Manufacturers of Lead Alkyls	5
1-4	Lead Alkyl Production Data	6
6-1	Acute Toxicity of Tetraethyl and Tetramethyl Lead to Fresh and Saltwater Organisms.	41
9-1	Toxicity Summary for Tetraethyl Lead	54
9-2	Toxicity Summary for Tetramethyl Lead.	55
9-3	Composite Scores for the Toxicity of Tetraethyl Lead	56
9-4	Composite Scores for the Toxicity of Tetramethyl Lead.	58
9-5	Minimum Effective Dose (MED) and Reportable Quantity (RQ). . .	62
9-6	Minimum Effective Dose (MED) and Reportable Quantity (RQ). . .	63
9-7	Carcinogenicity Testing of Tetraethyl Lead	66

LIST OF ABBREVIATIONS

AIB	α-Aminoisobutyric acid
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EC_{50}	Median effective concentration
FEL	Frank effect level
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LT_{50}	Median lethal time
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
ppm	Parts per million
ppt	Parts per trillion
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister-chromatid exchange
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The CAS Registry numbers, molecular weights and empirical formulas of several lead alkyls are presented in Table 1-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The lower tetraalkyl lead compounds, such as tetrabutyl, tetraethyl, tetramethyl and tetrapropyl lead, are colorless liquids with a faint, sweet odor (Malpass et al., 1981). They are soluble in many organic solvents, but considered insoluble in water. Appropriate physical properties are available only for tetraethyl and tetramethyl lead; these properties are listed in Table 2.

Chemically, the tetraorganolead compounds are decomposed to lead metal and free organic radicals at elevated temperatures or in the presence of light. Oxygen inhibits the thermal decomposition of tetraethyl lead, favoring oxide formation rather than release of the free metal (Shapiro and Frey, 1967).

1.3. PRODUCTION DATA

The only lead alkyls manufactured in substantial commercial amounts are tetraethyl, tetramethyl and tetra(ethyl-methyl) lead. The current manufacturers and their production capacities are listed in Table 1-3. Available production data are listed in Table 1-4 (U.S. EPA, 1977). Domestic production volumes of lead alkyls for 1982 and 1983 are as follows (USITC, 1983, 1984):

	(millions of pounds)	
	1983	1982
tetraethyl lead	146.3 (sales)	224.2
tetra(methyl-ethyl) lead	105.7	130.3

TABLE 1-1

Lead Alkyl CAS Numbers, Molecular Weights, Empirical Formulas and Structures

Lead Alkyl Synonym	CAS Number	Molecular Weight	Empirical Formula
Tetrabutyl lead tetrabutyl plumbane	1920-90-7	435.65	$C_{16}H_{36}Pb$
Tetraethyl lead tetraethyl plumbane TEL	78-00-2	323.45	$C_8H_{20}Pb$
Tetramethyl lead tetramethyl plumbane TML	75-74-1	267.35	$C_4H_{12}Pb$
Tetrapropyl lead tetrapropyl plumbane	3440-75-3	379.54	$C_{12}H_{28}Pb$
Triethyl lead triethyl plumbane triethyl lead hydride	5224-23-7	295.38	$C_6H_{16}Pb$
Trimethyl lead trimethyl plumbane	7442-13-9	253.30	$C_3H_{10}Pb$
Tripropyl lead tripropyl plumbane hydrotripropyl plumbane	3440-75-3	337.46	$C_9H_{22}Pb$
Trimethylethyl lead TMEL trimethylethyl plumbane	1762-26-1	281.31	$C_5H_{14}Pb$
Dimethyldiethyl lead DMDEL dimethyldiethyl plumbane	1762-27-2	295.38	$C_6H_{16}Pb$
Methyltriethyl lead MTEL methyltriethylplumbane	1762-28-3	309.41	$C_7H_{18}Pb$

TABLE 1-2

Physical and Chemical Properties for Tetraethyl and Tetramethyl Lead

Property	Description	Reference
	Tetraethyl Lead	
Melting point:	-136°C	Verschueren, 1983
Boiling point:	decomposes 110/200°C	Verschueren, 1983
	198-202°C	Hawley, 1977
	78°C (10 mm Hg)	Shapiro and Frey, 1967
Specific gravity:	1.6528 (20/4°C)	Shapiro and Frey, 1967
Vapor pressure:		
at 20°C	0.15 mm Hg	Verschueren, 1983
at 20°C	0.30 mm Hg	Weber et al., 1981
at 20°C	0.26 mm Hg (calculated from Antoine equation)	Feldhake and Stevens, 1963
at 25°C	0.38 mm Hg (calculated from Antoine equation)	Feldhake and Stevens, 1963
Water solubility in distilled water:		
at 0°C	0.20 ppm	Feldhake and Stevens, 1963
at 26.6°C	0.21 ppm	Feldhake and Stevens, 1963
at 31.5°C	0.25 ppm	Feldhake and Stevens, 1963
at 37.5°C	0.25 ppm	Feldhake and Stevens, 1963
at 20°C	0.8 ppm	Verschueren, 1983
Water solubility in seawater (filtered):		
room temperature	20 ppm	Robinson and Rhodes, 1980
	Tetramethyl Lead	
Melting point:	-27.5°C	Verschueren, 1983
Boiling point:	110°C decomposes	Verschueren, 1983
Specific gravity:	1.995 (20/4°C)	Shapiro and Frey, 1967

TABLE 1-2 (cont.)

Property	Description	Reference
	Tetramethyl Lead (cont.)	
Vapor pressure:		
at 20°C	22.5 mm Hg	Verschueren, 1983
at 20°C	22.5 mm Hg	Weber et al., 1981
Water solubility:		
in seawater	15 mg/ℓ (Pb)	Verschueren, 1983
in distilled	9 mg/ℓ	Tiravanti and Boari, 1979
Conversion factor (air):	1 mg/m^3 = 8.61 ppm as Pb	Verschueren, 1983

TABLE 1-3

United States Manufacturers of Lead Alkyls[a]

Manufacturer	Location[b]	Annual Capacity (millions of lbs)	Lead Alkyl
DuPont	Deepwater, NJ	143 29	tetraethyl lead tetramethyl lead
Ethyl Corp.	Baton Rouge, LA	231	tetraethyl lead
Nalco Chem. Co.	Freeport, TX	110	tetraethyl, tetramethyl and mixtures

[a]Source: SRI, 1984

[b]DuPont maintains capacity for tetraethyl lead blending at Antioch, CA. Ethyl Corp. maintains a blending facility at Pasadena, TX.

TABLE 1-4

Lead Alkyl Production Data[a,b]

Producer	Type of Production	Production Range (lbs)
Tetramethy lead		
Ethyl Corp. Baton Rouge, LA	manufacturer	confidential
DuPont Antioch, CA	manufacturer	1-10 million
Deepwater, NJ	manufacturer	confidential
Nalco Chem. Freeport, TX	manufacturer	confidential
Mobil Oil New York, NY	importer	0.1-1.0 million
Tetraethyl lead		
Ethyl Corp. Baton Rouge, LA	manufacturer	confidential
Pasadena, TX	manufacturer	confidential
PPG Industries Beaumont, TX	manufacturer	50-100 million
DuPont Antioch, CA	manufacturer	50-100 million
Deepwater, NJ	manufacturer	confidential
Nalco Chem. Freeport, TX	manufacturer	confidential
Esso Eastern Houston, TX	importer	10-100 thousand
Mobil Oil New York, NY	importer	0.1-1.0 million
Tetrapropyl lead		
DuPont Wilmington, DE	processor	confidential

TABLE 1-4 (cont.)

Producer	Type of Production	Production Range (lbs)
Tetrabutyl lead		
DuPont Wilmington, DE	processor	confidential
Trimethylethyl lead		
PPG Industries Beaumont, TX	manufacturer	1.0-10 million
DuPont Antioch, CA Deepwater, NJ	manufacturer manufacturer	1.0-10 million confidential
Nalco Chem. Freeport, TX	manufacturer	confidential
Dimethyldiethyl lead		
PPG Industries Beaumont, TX	manufacturer	10-50 million
DuPont Antioch, CA Deepwater, NJ	manufacturer manufacturer	10-50 million confidential
Nalco Chem. Freeport, TX	manufacturer	confidential
Methyltriethyl lead		
PPG Industries Beaumont, TX	manufacturer	10-50 million
DuPont Antioch, CA Deepwater, NJ	manufacturer manufacturer	10-50 million confidential
Nalco Chem. Freeport, TX	manufacturer	confidential

[a]Source: U.S. EPA, 1977

[b]No data were listed for triethyl, trimethyl or tripropyl lead.

Production of tetraethyl and tetramethyl lead is decreasing because restrictions on the amounts of lead allowed in gasoline as an additive and the increasing use of unleaded gasolines (CMR, 1982).

In the United States, tetraethyl and tetramethyl lead are manufactured by two major methods (Malpass et al., 1981; Hawley, 1977). The oldest and most commonly used method involves the alkylation of lead-sodium alloy with the appropriate alkyl chloride as shown by the reaction:

$$4NaPb + 4RCl \rightarrow R_4Pb + 3Pb + 4NaCl$$

where R=alkyl.

In 1963, Nalco Chemical Co. introduced production of tetraalkyl leads by an electrolysis method in which an alkyl Grignard reagent is used with an anode of lead pellets.

1.4. USE DATA

Virtually all of the lead alkyls manufactured are used as antiknock additives (octane boosters) in gasolines (Malpass et al., 1981; CMR, 1982). The amount of tetraalkyl lead added to gasoline varies with use; however, a typical regular leaded gasoline available at most commercial service stations contains ~0.8 g of tetraethyl lead per gallon (Lane, 1980).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of the lead alkyls in the environment will depend upon their ability to undergo chemical, photochemical and biological reactions, and to transport or partition from one environmental matrix into another. Most of the available data pertain to tetraethyl and tetramethyl lead.

2.1. WATER

2.1.1. Hydrolysis and Chemical Degradation. In dilute aqueous solution, tetraethyl and tetramethyl lead decompose to give a triethyl salt, then diethyl salt, and finally inorganic lead (Verschueren, 1983):

$$R_4Pb \rightarrow R_3Pb^+ \rightarrow R_2Pb^{2+} \rightarrow Pb^{2+}$$

where R is CH_3 or C_2H_5. Brown et al. (1375) estimated that the hydrolysis of tetraethyl lead in water of pH 7 at 40°C takes ~8 days for one half-life, to give $(C_2H_5)_3PbOH$.

In seawater, tetraethyl and tetramethyl lead are unstable (Maddock and Taylor, 1980). Degradation is rapid in the formation of trialkyl lead chloride; however, subsequent steps to form the dialkyl salt are considerably slower. The rate constants for the degradation of the tetraalkyl leads to trialkyl lead compounds in seawater have been reported as follows (Tiravanti and Boari, 1979):

tetraethyl lead	$k=1.33\times10^{-5}sec^{-1}$
tetramethyl lead	$k=1.83\times10^{-6}sec^{-1}$

The half-lives of tetraethyl and tetramethyl lead hydrolysis in seawater can be calculated to be 14.5 hours and 4.4 days, respectively. The triaklyl ions are quite stable in aqueous solution, but the dialkyl compounds degrade relatively rapidly to inorganic lead (Tiravanti and Boari, 1979).

Brown et al. (1975) estimated that tetraethyl lead is only slowly oxidized in water by RO_2, with a half-life of ~10^5 days.

2.1.2. Photolysis. The UV absorption spectra for both tetraethyl and tetramethyl lead show absorption up to ~340 nm (Harrison and Laxen, 1978a) which indicates a potential for direct photolysis; the authors have shown that these tetraalkyl leads undergo significant vapor-phase photolysis in the atmosphere.

Roederer (1981a, 1982) examined the photolytic decomposition of tetraethyl lead in laboratory vessels containing an aqueous medium. Illumination of the water solutions was found to result in the rapid degradation of tetraethyl lead into triethyl lead, which accumulated in the medium. Diethyl lead was formed in small amounts but did not accumulate; the concentration of inorganic lead increased slowly but continuously. In the dark, formation of triethyl lead reached a maximum of only 10% of that formed under illuminated conditions. Volatilization caused a considerable loss of initially added tetraethyl lead (Section 2.1.4.1.); however, illumination resulted in an increased amount of total Pb remaining in the aqueous phase. Therefore, the degradation of tetraethyl lead in the aquatic environment into its decomposition derivatives will apparently result in the extended persistence of organolead compounds (particularly triethyl lead) in the water phase. Charlou et al. (1982) reported the successive dealkylation of tetraethyl lead in seawater exposed to sunlight.

Jarvie et al. (1981) examined the degradation of tetraethyl and tetramethyl lead in aqueous medium exposed to sunlight. Both compounds were degraded rapidly, with initial half-lives of <2 days.

2.1.3. Microbial Degradation. Pertinent data regarding the microbial degradation of the lead alkyls in natural fresh or seawater, or in wastewaters or activated sludges were not located in the available literature cited in the Appendix.

2.1.4. Transport.

2.1.4.1. **VOLATILIZATION** -- Reoderer (1981a, 1982) observed the rapid loss of tetraethyl lead from laboratory vessels containing aqueous solutions of the compound. For example, after 98 hours of incubation, 99.5% of the total added lead was eliminated from aqueous solutions under nonilluminated conditions and 96% under illuminated conditions. Illumination resulted in photolytic decomposition to triethyl lead, which is apparently not as volatile as tetraethyl lead.

Feldhake and Stevens (1963) measured the equilibrium of water to gas-phase concentrations of tetraethyl lead over the range of temperatures 0-37.5°C. At 25°C, the gas-to-water ratio is ~30:1, which is the unitless Henry's Law constant; conversion to units results in a Henry's Law constant of ~0.7 atm-m³/mol. Calculation of Henry's Law constant from the water solubility (~0.21 ppm) and vapor pressure (~0.38 mm Hg) at 25°C yields a similar value of ~0.8 atm-m³/mol. These values of Henry's Law constants indicate that tetraethyl lead will volatilize rapidly from any environmental aquatic body in which it is in solution (Lyman et al., 1982).

Calculation of Henry's Law constant for tetramethyl lead from the water solubility (~9 ppm) and vapor pressure (22.5 mm Hg at 20°C) yields a value of 0.9 atm-m³/mol, which also indicates rapid volatilization.

2.1.4.2. **ADSORPTION** -- The relatively low water solubilities of tetraethyl and tetramethyl lead suggest that adsorption of the compounds to particulate matter and sediment in water is possible. Robinson and Rhodes (1980) examined the solubility of tetraethyl lead in filtered and in unfiltered seawater and concluded that alkyl lead compounds may adsorb and concentrate on suspended material in marine systems.

2.1.4.3. BIOACCUMULATION -- Tetraethyl lead has been found to bioaccumulate to potentially dangerous levels in eastern oysters (U.S. EPA, 1979). BCF values of 17,600 and 18,138 were found for exposures of 0.1 and 0.8 µg tetraethyl lead/ℓ, respectively, while tetramethyl lead showed little bioaccumulation at similar levels.

Maddock and Taylor (1980) determined BCF values for three marine species (shrimp, mussel and plaice) after a 96-hour exposure to LC_{50} concentrations of tetraethyl and tetramethyl lead. The results are summarized below:

Tetramethyl Lead	BCF
shrimp	20
mussel	170
plaice	60

Tetraethyl Lead	
shrimp	650
mussel	120
plaice	130

Tetramethyl lead can bioaccumulate to various residual levels in rainbow trout (Wong et al., 1981). Exposure to 3.5 µg tetramethyl lead/ℓ resulted in whole fish BCFs of 100 and 700 after 1 and 7 days, respectively.

Estimation of BCF can be made from WS data and use of the following equation derived by Kenaga and Goring (1978):

$$\log BCF = 2.791 - 0.564 \log WS \text{ (in ppm)}.$$

Assuming tetraethyl and tetramethyl lead water solubilities of 0.2 and 9 ppm, respectively, the respective BCFs are ~1530 and 180.

2.2. AIR

2.2.1. Chemical Removal. The atmospheric chemical removal processes include photolytic transformations, reaction with hydroxyl radicals, reaction

with other radicals and reaction with ozone (Cupitt, 1980). Data are available for these processes with regard to tetraethyl and tetramethyl lead.

2.2.1.1. PHOTOLYSIS -- Harrison and Laxen (1978a) experimentally determined photolysis rate constants (ke) for tetraethyl and tetramethyl lead under exposure to direct bright sunlight at solar zenith angles of 40° and 75°; these results and calculated half-lives are as follows:

	ke, z=40°	half-life (hours)	ke, z=75°	half-life (hours)
Tetraethyl lead	5.1×10^{-3}/min	2.27	1.29×10^{-3}/min	8.95
Tetramethyl lead	1.4×10^{-3}/min	8.25	3.38×10^{-4}/min	34.2

2.2.1.2. REACTION WITH OH -- The reaction of tetramethyl lead with hydroxyl radical probably occurs as (Harrison and Laxen, 1978a):

$$(CH_3)_4Pb + OH \rightarrow (CH_3)_3PbCH_2 + H_2O$$

Harrison and Laxen (1978a) determined the rate constants for OH reaction with tetramethyl and tetraethyl lead to be 13.3×10^9 and 11.7×10^9 $ppm^{-1}min^{-1}$ at 27°C, respectively. Assuming an average atmospheric OH concentration of 10^6 molecules/cm^3 (3.7×10^{-8} ppm), tetramethyl and tetraethyl lead half-lives of 23.3 and 2.7 hours, respectively, are calculated.

Nielsen et al. (1982) used a pulse radiolysis method of producing OH radicals to determine rate constants for tetramethyl and tetraethyl lead at 23°C to be 3.8 and 7.0×10^{12} cm^3/mole-sec. These rate constants can be used to calculate respective half-lives of 2.1 and 1.1 days, assuming an average atmospheric OH concentration of 10^{-18} moles/cm^3.

2.2.1.3. REACTION WITH OZONE -- Harrison and Laxen (1978a) reported the rate constants for the reaction of ozone with tetraethyl and tetramethyl

lead at 27°C to be 1.63-1.8x10^{-2} ppm^{-1} min^{-1} and 0.71-1.88x10^{-3} ppm^{-1} min^{-1}, respectively. Assuming an average atmospheric ozone concentration of 10^{12} molecules/cm^3 (3.7x10^{-2} ppm), tetraethyl and tetramethyl lead median half-lives of 0.8 and 10 days, respectively, are calculated. Assuming a similar ozone reaction mechanism with organotin compounds, the ozone reaction with tetramethyl lead may be represented as follows (Harrison and Laxen, 1978a):

$$Pb(CH_3)_4+O_3 \rightarrow (CH_3)_3PbOOH+CH_2O$$

2.2.1.4. REACTION WITH OTHER RADICALS -- The reaction of tetramethyl lead with $O(^3P)$ atoms may be represented by Equations 2-1 and 2-2, with Equation 2-2 being more probable (Harrison and Laxen, 1978a):

$$(CH_3)_4Pb+O \rightarrow (CH_3)_3PbO+CH_3 \qquad (2\text{-}1)$$

$$(CH_3)_4Pb+O \rightarrow (CH_3)_3PbCH_2+OH \qquad (2\text{-}2)$$

Harrison and Laxen (1978a) determined the $O(^3P)$ atom rate constants with tetraethyl and tetramethyl at 27°C to be 18.9x10^2 ppm^{-1} min^{-1} and 6.96x10^2 ppm^{-1} min^{-1}, respectively. Assuming an average $O(^3P)$ atmospheric concentration of 2.5x10^4 molecules/cm^3 (~10^{-9} ppm), tetraethyl and tetramethyl lead half-lives of 255 and 692 days, respectively, are calculated.

2.2.2. Physical Removal. The atmospheric physical removal processes include adsorption on aerosol particulates, dissolution (wet deposition) and dry deposition (Cupitt, 1980).

2.2.2.1. ADSORPTION -- Edwards and Rosenvold (1974) demonstrated that tetraethyl lead could undergo significant adsorption to atmospheric dust components during laboratory simulated air stream testing. Subsequent monitoring of the atmospheric aerosol in selected English locations found

that organolead compounds adsorbed upon particles amounted to 0.2-1.2% of the total particulate Pb in the atmosphere (Harrison and Laxen, 1977). Harrison and Laxen (1978a) tested the uptake of tetramethyl and tetraethyl lead on atmospheric particulates under a variety of laboratory conditions and found that both tetramethyl and tetraethyl lead may be adsorbed significantly under certain parameters, with tetraethyl lead having a more significant uptake than tetramethyl lead. Extrapolation to conditions in the urban atmosphere, however, suggest that adsorption to atmospheric aerosol particulates is not an important environmental sink process for the tetraalkyl leads.

2.2.2.2. **DISSOLUTION** -- During rainfall, inorganic lead is washed out of the atmosphere (Harrison et al., 1975; Lazrus et al., 1970); however, the relative water insolubility of tetraethyl and tetramethyl lead suggest that dissolution of these two compounds is not likely to be environmentally important. By monitoring rainwater drainage systems around gasoline-filling stations, Potter et al. (1977) indicated that washout of air around the stations does not contribute significantly to lead alkyl removal.

2.3. SOIL

Studies specific to the microbial or chemical degradation of the lead alkyls in soil were not located. Diehl et al. (1983) examined the behavior of tetraethyl and tetramethyl lead in soil pot experiments in which spring wheat was planted. In the soil, tetraethyl and tetramethyl lead were converted to water-soluble lead compounds that were toxic and readily available to the plants; decomposition of the tetraethyl and tetramethyl lead to lead was slow over a 3-month period. The water-soluble lead metabolites were found to be easily leached from the soil.

The K_{oc} of an organic compound may be estimated from its WS by use of the relationship developed by Kenaga and Goring (1978):

$$\log K_{oc} = 3.64 - 0.55 \log WS \text{ (in ppm)}.$$

Using tetraethyl lead (0.2 ppm) and tetramethyl lead (9 ppm) WS, respective K_{oc} values of 10,580 and 1300 are calculated. These K_{oc} values indicate that tetraethyl lead is nearly immobile in soil, while tetramethyl lead is only slightly mobile. Therefore, significant leaching of tetraethyl and tetramethyl lead is not expected to occur; however, water soluble metabolites of these compounds will leach. In addition, if other solvents are present, the mobility of the parent compound many be significantly enhanced.

As noted in Section 2.1.4.1., tetraethyl and tetramethyl lead in solution in the aquatic environment will volatilize rapidly into the air. Therefore, evaporation of these lead alkyls from the soil environment may occur; however, the high adsorption of tetraethyl and tetramethyl lead by soil may limit the overall significance of soil volatilization.

2.4. SUMMARY

With respect to the lead alkyls, data sufficient to predict environmental fate are available only for tetraethyl lead and tetramethyl lead. When exposed to the sunlit atmosphere, tetraethyl lead and tetramethyl lead are rapidly decomposed by a combination of direct photolysis, reaction with hydroxyl radicals and reaction with ozone. The half-life of tetraethyl lead in a brightly sunlit atmosphere is expected to be ~1 hour, while the half-life of tetramethyl lead will be on the order of several hours. Tetraethyl lead and tetramethyl lead are adsorbed by atmospheric particulates; however, this process is not expected to be an important environmental sink (Harrison and Laxen, 1978a).

In the aquatic environment, tetraethyl lead and tetramethyl lead are susceptible to significant hydrolysis, with rate of degradation accelerated by seawater. The degradation proceeds through a trialkyl to dialkyl to inorganic lead; in seawater, the initial degradation product is trialkyl chloride. Tetraethyl lead and tetramethyl lead are also susceptible to significant photolytic decomposition in water. Photolysis of tetraethyl lead can produce triethyl lead, which may be more environmentally persistent than tetraethyl lead. In aqueous solution, tetraethyl lead and tetramethyl lead both volatilize rapidly, making volatilization an important transport process. Tetraethyl lead and tetramethyl lead can be adsorbed by suspended particulate matter and sediment, which may extend the length of their persistence in water. Bioaccumulation of tetraethyl lead in aquatic organisms has been demonstrated.

Limited soil fate data indicate that tetramethyl lead and tetraethyl lead are converted into water soluble lead compounds in soil (Diehl et al., 1983). Tetraethyl lead and tetramethyl lead are not expected to leach significantly in soil, although their water soluble metabolites are subject to leaching.

3. EXPOSURE

3.1. WATER

Tetraethyl lead may enter the aquatic environment from waste streams generated during manufacturing processes (Gruber, 1975). In addition to anthropogenic sources, tetraalkyl lead may be generated in the aquatic environment by a combination of chemical/biological alkylation of inorganic or various organic lead compounds that may be exposed to appropriate conditions (Wong et al., 1975; Dumas et al., 1977; Schmidt and Huber, 1976; Jarvie et al., 1975; Harrison and Laxen, 1978b; Thompson, 1981; Chau and Wong, 1980).

Wong and Chau (1979) investigated the potential for indigenous microorganisms in certain aquatic sediments to methylate organic and inorganic lead compounds to volatile and toxic tetramethyl lead. They reported that methylation of organo-lead compounds occurred readily with and without sediment, but that methylation of inorganic lead was sporadic. Methylation also reportedly increased both the toxicity of lead to several species of freshwater algae and the bioaccumulation of lead to high levels in fish.

Chau et al. (1980) analyzed 32 water samples and 50 sediment samples from various lakes and rivers in Ontario, Canada, for the presence of tetraalkyl lead compounds; tetraalkyl leads were not detected in any sample. Potter et al. (1977) surveyed various natural waters in England for the presence of lead alkyls but did made no positive identifications.

Chau et al. (1984) detected the following lead alkyls in sediment taken from the St. Lawrence River near Maitland, Ontario (concentrations in ng/g as Pb, wet weight): methyltriethyl lead (142 ng/g), tetraethyl lead (329-1152 ng/g), triethyl lead^{+1} (187 ng/g) and diethyl lead^{+2} (22 ng/g).

The U.S. EPA Storet Data Base lists no observations for the lead alkyls.

3.2. FOOD

Sirota and Uthe (1977) detected tetraalkyl leads in Canadian cod, lobster, mackerel and flounder products at concentrations ranging from 0.01-4.79 ppm. Chau et al. (1979) detected tetramethyl lead in 1 of 50 fish samples analyzed from Canadian waters; concentration in the fillet was 0.26 µg/g.

Chau et al. (1984) detected the following lead alkyls in samples of carp, pike, white sucker or small mouth bass taken from the St. Lawrence River near Maitland, Ontario (concentrations in ng/g as Pb, wet weight): tetramethyl lead (137 ng/g), diethyldimethyl lead (57-96 ng/g), methyltriethyl lead (142-293 ng/g), tetraethyl lead (780-4384 ng/g), trimethyl lead^{+1} (95-2735 ng/g), dimethyl lead^{+2} (362 ng/g), triethyl lead^{+1} (53-3433 ng/g) and diethyl lead^{+2} (92-4268 ng/g).

3.3. INHALATION

In addition to emissions during tetraethyl and tetramethyl lead manufacture, tetraalkyl leads are exposed to the atmosphere by automotive emissions and by evaporative losses during filling of gasoline tanks, gasoline spillage, and other leaded gasoline-related exposures (Harrison and Laxen, 1978a; DeJonghe et al., 1981). Harrison and Laxen (1978a) reported that tetraalkyl lead is also emitted to the atmosphere due to methylation of lead compounds in the environment.

Six air samples collected in Baltimore, MD, during 1977 were found to have mean tetraethyl and tetramethyl lead concentrations of 6.8 and 3.5 ppt, respectively (Brodzinsky and Singh, 1982). Radziuk et al. (1979) sampled air in Toronto, Canada, 3 m above ground and 5 m from a relatively busy urban street. The following lead alkyl concentrations (in ng Pb/m^3) were detected: trimethyl-ethyl lead, 1; dimethyldiethyl lead, 2; methyltriethyl lead, 1; and tetraethyl lead, 8.

DeJonghe et al. (1981) monitored the air in Antwerp, Belgium, near gasoline stations, residential areas, underground tunnels, car repair shops and various streets for individual tetraalkyl leads. In addition to tetraethyl and tetramethyl lead, trimethylethyl lead, dimethyldiethyl lead, and methyltriethyl lead were also detected. Lead alkyl concentrations varied from 0.3 ng/m³ in a rural environment to 400 ng/m³ near a gas station.

Harrison and Laxen (1978b) reported the following typical values of tetraalkyl lead concentrations in air:

	Concentration (ng/m³)
urban air	<6-206
petrol stations	210-590
underground car park	1800-2200
rural air	0.5-230

3.4. DERMAL

Pertinent data regarding dermal exposure to lead alkyls were not located in the available literature cited in the Appendix. Dermal exposure is possible during operations involving leaded gasolines, such as filling gasoline tanks.

4. PHARMACOKINETICS

4.1. ABSORPTION

Information regarding the absorption of lead alkyls from the GI tract is limited. The U.S. EPA (1984a) reviewed data which suggest that the tetraalkyl leads would be converted to their trialkyl forms in acidic gastric secretions. The trialkyl compounds are expected to be absorbed extensively from the gastrointestinal tract.

The absorption of tetraethyl and tetramethyl lead following inhalation was studied in a group of volunteers exposed to the radiolabeled compounds at ~1 mg/m³ (Heard et al., 1979). Subjects breathed the vapor through a mouthpiece, taking 10-40 breaths of ~1 ℓ volume. Absorption was ~37 and 51% of the inhaled dose for tetraethyl and tetramethyl lead, respectively. Exhalatory loss during 48 hours post-treatment was ~20 and 40% of the deposited tetraethyl and tetramethyl lead, respectively. Absorption of tetraethyl lead by rats following inhalation exposure at 0.07-7.0 mg/ℓ was 16-23% of the inhaled dose (Mortensen, 1942). Morgan and Holmes (1978) reported that ~20-25% of radiolabeled lead in engine exhaust (radiolabeled tetraethyl lead was added to the fuel) was absorbed by the lungs in rats exposed by inhalation. The lead containing compound(s) in the exhaust fumes were not identified.

Percutaneous absorption of tetraethyl and tetramethyl lead represents a significant route of exposure. Both compounds were absorbed rapidly and relatively efficiently through the skin of rats and rabbits (Kehoe and Thamann, 1931; Laug and Kunze, 1948). Toxicity occurred rapidly after dermal exposure. Laug and Kunze (1948) reported that absorption of tetraethyl lead was 6.5% following dermal exposure and a significant portion of the dose was lost by evaporation. Davis et al. (1963) indicated that dermal absorption of tetramethyl lead was slower than that of tetraethyl lead.

4.2. DISTRIBUTION

Following absorption, tetraethyl and tetramethyl leads are rapidly carried by the blood, in plasma and erythrocytes, and distributed throughout the body. Soon after absorption, the tetraalkyl lead compounds are converted to their trialkyl forms (Section 4.3.) so that much of the distributed compounds are triethyl and trimethyl lead. In contrast to inorganic lead, a larger fraction of alkyl lead appears to be carried in plasma (Heard et al., 1979), but partitioning of trialkyl lead between erythrocytes and plasma appears to depend upon the trialkyl lead in question and the species. Byington et al. (1980) found that washed human erythrocytes *in vitro* had a low affinity for triethyl lead; however, the ratio of the *in vitro* binding of triethyl lead to the globin moiety of rat erythrocytes was three molecules per hemoglobin tetramer. Rabenstein et al. (1981), however, found that trimethyl lead rapidly crossed the membrane of intact human erythrocytes *in vitro* and became complexed with erythrocyte glutathione. In volunteers exposed to tetramethyl and tetramethyl lead by inhalation at ~1 mg/m^3, blood levels of radiolabeled lead (^{203}PB) fell to <1% of levels during exposure within 10 and 4 hours, respectively (Heard et al., 1979). Heard et al. (1979) reported that tetramethyl lead is rapidly transferred from the lungs through the blood to other tissues, with a blood half-time of only 13 seconds. The more water soluble trialkyl forms may exist in the blood for longer periods. At 1 hour after inhalation of tetraethyl lead, 50% of the radiolabel was in the liver, 5% in the kidneys and the remainder scattered throughout the body. Distribution of tetramethyl lead was similar. Levels of radioactivity in the brain were not very different from levels in the whole soft tissue exclusive of liver and kidney. As reviewed by Grandjean and Nielsen (1979), brain levels of lead

(presumably as triethyl lead) in three individuals who died from acute tetraethyl lead poisoning were 11.0 μg/g we weight (Bolanowska et al., 1967), 7.4 μg/g wet weight (Cassels and Dodds, 1946) and 10.0 μg/g wet weight (Kehoe, 1976). Nielsen et al. (1978) reported a median level of trialkyl lead of 0.014 μg/g wet weight in the brains obtained at autopsy of 22 individuals who had resided in Copenhagen. Persons who had lived on upper floors had ~4 times greater brain levels than did individuals residing on lower floors or suburbs. The difference reflected the degree of atmospheric pollution.

In rats exposed to exhaust particulates containing tetraethyl lead, distribution of radiolabeled lead (^{203}Pb) was followed from 2 minutes through 190 hours after exposure (Morgan and Holmes, 1978). Blood and liver levels reached a maximum at 1.3 hours after exposure. Kidney levels accounted for 10-11% at 20-21 hours post-exposure and lung levels gradually decreased throughout the post-exposure sample period. The liver contained a maximum of 6.8% of the total dose. Much of the lead appeared to be associated with the GI tract (36.7% after 1.6 hours) or distributed generally throughout the carcass (~20% of dose throughout the test period).

Bolanowska (1968) administered tetraethyl lead to rats by intravenous injection and analyzed blood and tissue samples for triethyl lead. The conversion from tetra to triethyl lead was rapid. Within 24 hours, 50% of the administered tetraethyl lead was recovered as triethyl. Levels of triethyl lead were highest in the liver with decreasing concentrations in the blood, kidney and brain. Similar distribution was reported in rabbits treated with tetraethyl lead by intraperitoneal injection (Yamamura et al., 1979). Tissue levels of triethyl lead in the liver, kidney, brain, skeletal muscle, cardiac muscle, spinal cord and blood (in decreasing lead content)

were highest at 24 hours after treatment with tetrathyl lead. The half-time for triethyl and trimethyl lead in tissues is relatively long, with trimethyl lead being more persistent than triethyl (Hayakawa, 1972). Hayakawa (1972) reported a half-time of 7-8 days for triethyl lead in the brain of rats, and a much longer interval for trimethyl lead. Yamamura et al. (1975) determined half-times of 35 and 100 days in a two-compartment model for retention of triethyl lead in humans.

4.3. METABOLISM

Tetraalkyl lead compounds undergo oxidative dealkylation to trialkyl lead soon after absorption. The trialkyl leads are regarded as the actual toxic forms (U.S. EPA, 1984a). Initially, hydroxylation of the tetraalkyl lead occurs, which is mediated by p-450 dependent mono-oxygenases (Ferreira da Silva et al., 1963). The hydroxyl metabolite is an intermediate that allows dealkylation to the trialkyl lead. Deethylation of tetraethyl lead occurred at a maximum rate of 200 µg/g liver tissue/hour in rats. Demethylation of tetramethyl lead appears to be somewhat slower in rats and more rapid in mice (Cremer, 1959; Cremer and Callaway, 1961). Dealkylation appears to proceed by a similar process in rats, mice, rabbits and humans (U.S. EPA, 1984a). Tetraalkyl leads were dealkylated to trialkyls, in decreasing order of activity, by preparations of liver, kidney and brain in rats and rabbits (Bolanowska and Wisniewska-Knypl, 1971). The trialkyl lead compounds may be further dealkylated to dialkyl forms in rabbits and humans (U.S. EPA, 1984a). Prough et al. (1981) reported that *in vitro* tetraethyl lead and triethyl lead acetate were metabolized so that ethylene and ethene were formed, indicating dealkylation in both. Rabenstein et al. (1981) reported that trimethyl lead complexes with glutathione in solution and in human erythrocytes. *In vivo*, the glutathione content in the brains of rats

treated orally with triethyl lead was decreased in a dose-related manner (Chand and Clausen, 1982). In vitro, however, these researchers found no conjugation of triethyl lead with glutathione in the absence or presence of brain cytosol.

4.4. EXCRETION

Excretion of alkyl lead compounds has been reported, from the lungs (Heard et al., 1979), urine (Grandjean and Nielsen, 1979; Arai et al., 1981; Bolanowska, 1968; Yamamura et al., 1981), feces (Bolanowska, 1968; Arai et al., 1981) and bile (Arai et al., 1983). Elimination via the lungs was reported in volunteers inhaling tetraethyl and tetramethyl lead. About 40 and 20%, respectively, of the absorbed tetramethyl and tetraethyl lead was exhaled within 48 hours after exposure. The ratio of remaining radioactivity excreted in the feces versus the urine was 1:8 for tetraethyl lead and 1:0 for tetramethyl lead.

Urinary metabolites found in rats treated by intravenous injection with tetrethyl lead included triethyl lead (1% of dose) and inorganic lead (Bolanowska, 1968). Arai et al. (1981) reported that rabbits given tetraethyl lead by intraperitoneal injection excreted diethyl lead (69%), inorganic lead (27%) and triethyl lead (4%). In workers exposed to tetraethyl lead compounds, urinary excretion of triethyl lead accounted for about 10% of urinary lead (U.S. EPA, 1984a). Yamamura et al. (1981) reported that in humans with tetraethyl lead poisoning, urinary lead comprised ~50% diethyl lead, 48% inorganic lead and ~2% triethyl lead when measured 28 days after exposure.

Biliary lead collected from rabbits given an intraperitoneal dose of 12 mg tetrethyl lead accounted for ~12% of the injected dose. Diethyl lead accounted for ~97% of the biliary lead (Arai et al., 1983). Lead detected in

the feces at 2 days after treatment was 85% inorganic lead, 9% diethyl lead and ~6% triethyl lead (Arai et al., 1981, 1983). At 7 days after dosing fecal lead was 95% inorganic, 4% triethyl and ~1% diethyl lead.

The rate of elimination of alkyl lead compounds and metabolites is relatively slow. Yamamura et al. (1975) reported that a two-compartment model best fit the excretion profile of triethyl lead in humans, having half-times of 35 and 100 days, respectively. Heard et al. (1979) reported that based on urinary excretion of lead from poisoning cases, half-lives for the tetraalkyl leads were <150 days. Based on urinary excretion rates in volunteers over 200 hours post-inhalation, Heard et al. (1979) suggested that the mean retention time of metabolites and organic lead would be 300-500 days.

5. EFFECTS

As discussed in Chapter 4, the tetraalkyl leads are metabolized by mammals to neurotoxic trialkyl leads and further dealkylated products, including inorganic lead. Therefore, exposure to lead alkyls may result in toxic effects similar to those of inorganic lead. The effects of inorganic lead exposure have been reviewed extensively by U.S. EPA (1984a); the following discussion considers only those studies in which the effects of exposure to lead alkyls per se were assessed.

5.1. CARCINOGENICITY

In humans exposed to tetraethyl lead for $\geq$20 years, Robinson (1974, 1976) found a slight but not significant increase in the number of skin cancers (7/139) compared with a matched-control group (4/139). These cases occurred among workers still employed by the company; a mortality analysis of workers who left employment because of illness or retirement was not performed. Therefore, the carcinogenic risk of chronic occupational exposure to tetraethyl lead is not adequately tested by this study.

As reviewed by Grandjean and Andersen (1982), Haring (1980) reported preliminary results of a mortality study of workers exposed to tetraethyl lead that suggested a 10-fold increase in the incidence of multiple myeloma compared with expected numbers. Additional data from this report were not available and a final publication of the study was not located.

Kantor et al. (1979) conducted a retrospective case control study of 149 cases of Wilms' tumor in children by examining the Connecticut tumor registry and attempted to correlate the condition with occupational exposure of the fathers. Of the 149 children with Wilms' tumor, 22 had fathers with occupations related to lead exposure. Of the 149 matched control children

without the tumor only 6 had fathers with lead related occupational exposure. The difference was significant ($p<0.05$). The extent of the occupational exposure was not reported. An association with "hydrocarbon related" occupations and Wilms' tumor cases was also suggested (24 vs. 10). There is insufficient evidence from this study to suggest an association between paternal alkyl lead exposure and Wilms' tumor in childhood.

Tetraethyl lead was given in tricaprylin subcutaneously to random-bred Swiss mice of both sexes 1-4 times from birth to 21 days of life. All 69 of the litters which received 2 mg/animal died. Ninety-two percent (number not given) of those receiving 1.2 mg accumulated over 4 doses died. Twenty-two percent of those receiving 0.6 mg over 4 doses also died. Among the 41 female survivors, 5 of them developed malignant lymphomas between 36 and 51 weeks. There were no malignant lymphomas in 48 control females. In males, malignant lymphomas occurred in 1/26 animals exposed to the lower dose compared with 1/39 control animals. The working group of IARC felt that a further study is warranted (IARC, 1980).

5.2. MUTAGENICITY

In mutagenicity tests using Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100, tetramethyl lead had no activity in plate tests with or without metabolic activation (Haworth et al., 1983). Ahlberg et al. (1972) reported that diethyl lead chloride, triethyl lead chloride, dimethyl lead chloride and trimethyl lead chloride treatment of Allium cepa (onion) root tips resulted in significantly increased percentages of spindle disturbances during meiosis. Triethyl lead chloride treatment of Drosophila melanogaster significantly ($p<0.001$) increased the incidence of XO exceptions, indicating chromosome loss due to breakage. There was no effect on

the incidence of XXY exceptions, precluding nondisjunction of the sex chromosome. The other lead alkyls were not tested in D. melanogaster.

Trialkyl leads, as reported in a brief note, increased SCE in human lymphocytes, in vitro (Grandjean and Andersen, 1982). Kennedy and Arnold (1971) reported no increase in dominant lethal mutations was evidence in mice treated with tetraethyl lead. The limited data, available are insufficient for drawing any conclusion regarding the mutagenic activity of alkyl lead compounds.

5.3. TERATOGENICITY

Tetraethyl lead was administered by oral intubation (in corn oil) to pregnant CD-1 mice and COBS rats at 0.01, 0.10, 1.00, and 10.0 mg/kg on days 5-15 (for mice) or 6-16 (for rats) of gestation (Kennedy et al., 1975). Groups of 20 females of each species were exposed at each dose level and as vehicle controls. Dams were sacrificed on day 18 (mice) or day 20 (rats) for examination of uteri and fetuses. Maternal toxicity was severe following treatment at 1.0 and 10.0 mg/kg tetraethyl lead, with 25% (mice) and 70% (rats) decreased weight gain during gestation at the low dose and tremors, convulsions and hypoactivity at the highest dose level. Because of severe maternal weight loss treatment at 10 mg/kg was discontinued after three daily doses. The number of pregnancies among female mice treated at 10 mg/kg was sharply reduced (5/20 vs. 15-20/20 among other dose groups and controls). There was no significant effect on the number of implantation sites among dams treated at any dose level. The number of resorption sites was increased and the number of and live fetuses was decreased among dams treated at 1.0 and 10.0 mg/kg. Three abnormal fetuses (3/238) were observed among litters exposed at 0.1 mg/kg, while none occurred among litters exposed at other treatment levels and 2/174 were reported among the vehicle

control group. In rats, the number of pregnant females among those exposed at 10.0 mg/kg was reduced (7/20 vs. 15-20/20 among other treatment groups and controls). There was also a reduction in the number of implantation sites per pregnant dam among rats of the high dose group. Resorption sites were increased and live fetuses per litter were decreased among groups treated at 1.0 and 10.0 mg/kg. A single abnormal fetus was observed in each of the groups exposed at 0.01 and 0.1 mg/kg (1/178 and 1/238, respectively), while none occurred among the two higher dose groups. In control litters, two abnormal fetuses occurred among 184 live fetuses. Mean fetal weights were significantly ($p<0.05$) reduced in males and females of both species treated at 1.0 and 10.0 mg/kg, while fetal weights among groups treated at lower doses were comparable with vehicle controls.

The teratogenic effects of tetraethyl and tetramethyl lead and trimethyl lead chloride were tested by oral administration in Sprague-Dawley rats (McClain and Becker, 1972). The compounds were administered at several dose levels: 7.5, 15 or 30 mg/kg for tetraethyl lead; 40, 80, 112 or 160 mg/kg for tetramethyl lead; and 15, 30 or 38 mg/kg for trimethyl lead chloride, during early organogenesis (days 9, 10 and 11 of gestation) or during late organogenesis (days 12, 13 and 14). Trimethyl lead chloride was also administered by intravenous injection at 20, 28, 33 or 40 mg/kg on days 8-15 of gestation. In all cases the highest dose level was lethal to the dams. At lower doses, maternal toxic effects ranged from slight (hyperexcitability and weight loss) to severe (tremors, spasticity and paralysis) in a dose-related manner. An increased number of resorption sites was reported among dams treated with 15 mg/kg tetraethyl lead and 112 mg/kg tetramethyl lead on days 9-11. Delayed fetal development was noted in almost all treatment groups for all compounds and included decreased crown-rump length, reduced

body weight and delayed ossification. There were, however, no significant skeletal deformations or soft tissue abnormalities among fetuses of treated rats.

Studies by Cragg and Rees (1984) and Ferris and Cragg (1984) examined the effects of tetramethyl leads on fetal and neonatal neuronal and brain development by administering the compound during gestation and early postnatal life. Tetramethyl lead (22 mg/kg bw/injection) was administered by subcutaneous injection to pregnant Long-Evans rats on days 7, 14 and 21 of gestation and to their neonatal pups on days 7 and 14 after birth. Birth weight of neonates was not affected by in utero exposure to the tetramethyl lead. Histological studies showed no apparent effect on brain myelination: dendrite growth, granule-cell production or retinal receptor development. Decreased brain weight, resulting in a higher body:brain weight ratio, was reported and is consistent with the neurotoxic effect of alkyl lead compounds (Sections 5.5. and 5.6.).

5.4. OTHER REPRODUCTIVE EFFECTS

Odenbro et al. (1982) intraperitoneally injected female NMRI mice with triethyl lead at 3.0 or 6.0 mg/kg on days 3 and 4 of gestation and measured plasma progesterone and estradiol levels at the time of blastocyst implantation. Progesterone levels were significantly ($p<0.025$) reduced in females treated at both dose levels, while estradiol levels were significantly reduced only in dams treated at 6.0 mg triethyl lead/kg bw. The decreased titer of these hormones may have ramifications on the decreased implantation and reduced reproductive capacity reported by other researchers (see Section 5.3.) since both hormones are involved in blastocyte implantation.

The effect of triethyl lead exposure on placental amino acid transfer was studied in Dunkin-Hartley guinea pigs by Kihlstrom and Odenbro (1983).

Pregnant dams were given triethyl lead chloride at 1.0 or 2.5 mg/kg bw (intraperitoneal injection) on day 62 or 63 of pregnancy (68-day term) and *in situ* placental transfer of AIB was determined the following day. Triethyl lead at 2.5 mg/kg reduced the transfer of AIB across the placenta, while 1.0 mg/kg had no effect. Decreased placental transfer of amino acids may result in reduced fetal growth (see Section 5.3.).

5.5. CHRONIC TOXICITY

Long-term studies on the toxic effects of alkyl leads are limited. In a 20-week study, Schepers (1964) administered tetramethyl and tetraethyl lead in peanut oil by gavage to groups of 12 CD rats (6/sex). Tetramethyl lead was given at 1.08 and 0.011 mg/kg, while tetraethyl lead was given at 0.0017 and 0.17 mg/kg on 5 days/week (100 total doses). A group of 16 vehicle control rats was maintained for comparison. Rats were sacrificed within 2 days of the last treatment and were examined for gross and histological toxic effects. Hyperactivity and irritability were observed among rats treated at the higher dose levels of both compounds. No mortality occurred during the study and body weights of rats treated with either tetraalkyl lead compound were similar to those of control rats. In rats treated at both dose levels of tetraethyl and tetramethyl lead, gross observation revealed swollen and friable livers and plaques with partial fatty replacement of the thymus. Hyperemia and edema of the brain and spinal cord were reported in 11/12 and 7/12 rats treated at 1.08 and 0.0011 mg/kg tetramethyl lead. Histological preparations revealed hepatocyte vacuolization and cytoplasmic degeneration and minimal neuronal damage among rats treated at 0.0017 mg tetraethyl lead. Rats exposed at 0.17 mg/kg developed similar but more severe histopathologies in the liver and brain (degeneration and deformity of nerve

tracts, nuclear pyknosis). Rats treated with tetramethyl lead at both dose levels developed hepatocyte cytoplasmic degeneration and vacuolization as well as neuronal degeneration, deformity and neuronophagia.

The toxicity of tetraethyl and tetramethyl lead to rhesus monkeys following oral administration at 6 µg/kg/day for 6 months was studied by Heywood et al. (1979). Groups of two male and two female monkeys were given the test solutions or a toluene/ethanol mixture (vehicle controls). No signs of toxicity were evident in any treated monkeys. Food consumption, body weight, behavior, hematological and biochemical parameters, organ weights, and macroscopic and microscopic examinations for pathologies were normal. Blood-lead levels in monkeys treated with tetraethyl lead increased during the study, indicating a potential for accumulation, while blood lead among monkeys given tetramethyl lead at 6 µg/kg/day was comparable with controls.

Davis et al. (1963) conducted a subchronic inhalation study of tetramethyl and tetraethyl lead in rats. Groups of 10 rats (5/sex) were exposed at 12, 22, 49 or 63 mg/m³ tetramethyl lead or 0, 12, 22 or 46 mg/m³ tetraethyl lead for 7 hours/day, 5 days/week. Irritable behavior was the first sign of toxicity after inhalation of both chemicals, followed by uncoordinated and combative behavior. At higher exposure levels, rats developed convulsions and died in a comatose state. Mortality was 9/10, 9/10 and 8/10 among rats exposed at 63 mg/m³ tetramethyl lead for 10 days, 49 mg/m³ for 18 days and 22 mg/m³ for 35 days, respectively. Rats exposed at 12.0 mg/m³ tetramethyl lead were maintained for 150 exposures, at which time 4 of 5 males and no females had died. Deaths among these males was apparently due to infection and was not dose-related. Mortality was 8/10 among rats exposed at 46 mg/m³ tetraethyl lead within 5 days of exposure and 9/10 by

day 14 in rats exposed at 22 mg/m³. Exposure at 12 mg/m³ was continued for 150 days with no mortality. Histopathological examination of animals that died during the study or those sacrificed after 150 days of exposure revealed lesions in the brain and spinal cord, liver, kidneys and lungs. The severity of toxic effects following exposure to both tetraalkyl lead compounds was related to level and duration of exposure, but the extent of toxic effects among rats exposed for 150 days was not specified. Toxic effects in general included the following: cerebral cortical and medullary necrosis, degeneration and "clumping and shrinkage of cells;" hepatocyte degeneration, swelling and nuclear enlargement; swelling and necrosis of the convoluted tubule epithelium and vacuolar degeneration of collecting tubules in the kidney; and small hemorrhagic lesions and general edema of the lungs (Davis et al., 1963).

The toxicity of inhaled tetramethyl and tetraethyl lead to Beagle dogs was also determined by Davis et al. (1963). Dogs were exposed at 44 (n=1), 23 (n=1), 12 (n=2) and 4 (n=2) mg/m³ tetramethyl lead or 42 (n=1), 22 (n=1) and 12 (n=2) mg/m³ tetraethyl lead (7 hours/day, 5 days/week). Dogs exposed at $\geq$12 mg/m³ tetramethyl lead died within 15 days of exposure, while those exposed at 4 mg/m³ died after 84 and 107 exposures. All dogs exposed to tetraethyl lead (at 12-42 mg/m³) died by 30 days of exposure. Histological effects were similar to those reported among rats (brain, liver, kidney and lung lesions), but details of specific dose-related effects were not available. This study (Davis et al., 1963) clearly demonstrated the increased sensitivity of dogs to the tetraalkyl lead compounds, compared with rats.

In a Polish study (Przybylowski et al., 1977) available as an English abstract, rabbits were exposed to leaded and unleaded gasoline for 6 months

to determine the toxic effects of tetraethyl lead as a fuel additive. Exposure was at 60 mg/ℓ gasoline for 4 hours/day, 6 days/week for 6 months. Similar effects (decreased serum and liver monoamine oxidase and increased liver and lung glyoxalase) occurred among rabbits exposed to both leaded and unleaded gasoline. The authors concluded that tetraethyl lead did not appear to contribute to the toxic effects of gasoline.

A study of lead intoxication among children who sniffed gasoline was conducted by Boeckx et al. (1977). Among two groups of children (n=43 and 50) with chronic gasoline-sniffing habits, mean aminolevulinic acid dehydrogenase levels were ~30% that of controls and decreased enzyme activity correlated with frequency of exposure. Cases of acute lead intoxication from chronic gasoline sniffing have shown lowered hemoglobin, increased urinary aminolevulinic acid and coproporphyrin and basophilic stippling (Boeckx et al., 1977; Robinson, 1978). Based on urine samples and hematological effects, inorganic lead as a metabolite of the tetraalkyl lead was regarded as the toxic compound.

In an English abstract of a Russian study, Korenev (1970) reported that symptoms of chronic poisoning from occupational exposure to tetraethyl lead

> "included autonomic dysfunction, sympathetic-adrenal stress, hyperesthemic neurosis-like syndrome, myoasthenic syndrome, vascular hypotonia, bradycardia, and hypothermia."

5.6. OTHER RELEVANT INFORMATION

Following oral administration to rats, tetraethyl and tetramethyl lead had single-dose LD_{50} values of 12.3-14.18 mg/kg (Schroeder et al., 19 a,b) and 110 mg/kg (Cremer and Callaway, 1961), respectively. The inhalation LC_{50} values for tetraethyl and tetramethyl lead were 850 and 8870 mg/m³ (Cremer and Callaway, 1961). Following intraperitoneal injection,

the acute toxicity in decreasing order was triethyl lead, tetraethyl lead, trimethyl lead and tetramethyl lead (Hayakawa 1972). Kawamori et al. (1983) reported that LT_{50} values for exposure to 20, 40, 60 and 80 mg/kg of tetraethyl lead by intraperitoneal injection were 149, 60, 47 and 39 minutes, respectively.

In an acute toxicity study, Heywood et al. (1978) administered tetraethyl and tetramethyl lead by intravenous injection to groups of two male and two female rhesus monkeys at t mg/kg/day for 7 days with a 10-day recovery period. Groups were also injected with 0.6 mg/kg/day tetraethyl lead or 1.2 mg/kg/day tetramethyl lead for 7 days, at which time doses were doubled and given for an additional 7 days. One male and one female of each group were sacrificed after the 14 days of treatment, while survivors were maintained until 28 days. Three of the four monkeys given 6 mg/kg/day tetraethyl lead were killed on days 4 or 5; severe toxic symptoms included hypoactivity and muscle tremors, marked body weight loss, reduced food intake and abnormal patellar reflex. Histological changes among monkeys treated at 6 mg/kg/day included skeletal muscle degeneration, peripheral axonal degeneration, reduced hepatic glycogen, fat deposition in renal cortical tubules and depressed brain cholinesterase activity (62% of controls). Depression of the grasp reflex was seen in 2 of 4 monkeys given 0.6-1.2 mg/kg/day tetraethyl lead. In monkeys given tetramethyl lead, a depressed patellar reflex was reported in 2/2 and 3/4 monkeys exposed at 6 and 1.2-2.4 mg/kg/day, respectively. Monkeys treated at the highest level were nervous and hyperexcitable. Both monkeys killed during the exposure period to 6 mg/kg/day tetramethyl lead showed peripheral axonal degeneration and skeletal muscle degeneration. No histological changes were observed among monkeys exposed at 1.2-2.4 mg/kg/day (Heywood et al., 1978).

Altered behavioral responses have been produced in rats treated with tetraethyl lead (Matsui et al., 1984) and triethyl lead (Booze et al., 1983). The frequency of lever pressing for food decreased in rats given tetraethyl lead at 10, 20 and 40 mg/kg by single intraperitoneal injection (Matsui et al., 1984). Other changes in behavioral patterns were reported but not specified. In neonatal rats exposed to triethyl lead by maternal dosing (3 or 6 mg/kg by subcutaneous injection), olfactory descrimination was impaired and nipple attachment was decreased. Neonates also developed slight body tremors, and high dose male neonates were hypoactive while low dose females were hyperactive.

In an English abstract of a Polish study, Karkos and Sikora (1973) reported neuronal degeneration in rats exposed to leaded gasoline (10 mg/ℓ hydrocarbon) containing 0.025 mg/ℓ Pb for 6 hours/day for 6 days. Degenerative changes occurred in the rhinencephalon, hypothalamus, reticular formation and neocortical ovas. Glial cell hyperplasia, lesions of the myelin sheath and vascular lesions were also reported. The authors suggested that gasoline hydrocarbons and tetraethyl lead had a synergistic effect on the CNS.

Several researchers (Akai et al., 1982; Niklowitz, 1974; Konat and Clausen, 1976) have indicated that acute exposure to tetraethyl lead leads to histological changes of nerve cells within the CNS. In rats treated by intraperitoneal injection with 10, 20, 40, 60 or 80 mg/kg tetraethyl lead for 2-7 days, extensive hydropic degeneration was observed in the cerebrum, cerebellum and spinal cord. Necrosis of the hippocampus occurred following treatment at >20 mg/kg/day (Akai et al., 1982). In rabbits, tetraethyl lead injected intraperitoneally at 100 mg/kg produced convulsions and histological changes in the brain with a latency of 12-18 hours. Lesions were seen

in astroglial and pyramidal cells as well as neural degeneration and subcellular changes (Niklowitz, 1974).

Triethyl lead was administered to neonatal rats by intraperitoneal injection on days 14, 16 and 18 (group A) or days 20, 22 and 24 (group B) to determine its toxic effects during the period of myelination onset or maximal myelin deposition (Konat and Clausen, 1976; Konat et al., 1976, 1979). Retardation of growth occurred in both treatment groups. In group A, forebrain lipid synthesis was inhibited. In group B, deposition of myelin was inhibited and depletion of sulfatides from myelin was observed. In rats treated only on days 20 (8 mg/kg) and 24 (5 mg/kg), the deposition of membrane in the formation of myelin was inhibited, while deposition of the lipid fraction of myelin was altered less significantly. The formation of protein involved in myelin membrane formation was inhibited, while total brain protein formation was less affected, indicating a specificity to myelin proteins (Konat et al., 1979). Triethyl lead treatment did not alter the relative concentrations of five major protein components of myelin (Konat and Clausen, 1978).

Effects of tetraethyl lead on the kidney were examined in rabbits given 100 or 200 mg/animal (2.5 kg bw) by single intraperitoneal injection (Chang et al., 1980). Animals were sacrificed at the onset of toxicity (hyperirritation, tremors and convulsions) and the renal cortex was prepared and examined with an electron microscope. Pathological changes were not evident at the light microscopy level, but ultrastructural cytopathological changes in the proximal tubule epithelium were noted. Altered subcellular changes were noted in lysosomes and rough endoplasmic reticulum, which may suggest changes in protein synthesis.

In humans acutely poisoned with tetraethyl lead by sniffing leaded gasoline, toxic symptoms include nervous irritability, tremors, nausea, vomiting and delirium. One death was reported. Many cases involve chronic sniffing habits; exposures may be very brief and more frequent during spring and summer. Gasoline sniffing was correlated with poor school behavior and delinquent behavior (Ross, 1982; Coulehan et al., 1983).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity of the lead alkyls to aquatic biota has been investigated for three species of fish and two species of invertebrates (Table 6-1). All vertebrate and invertebrate toxicity data are limited to exposure with the tetraalkyl leads, those exhibiting the greatest potential for harm to the environment.

Turnbull et al. (1954) reported 24- and 48-hour static LC_{50} values of 2.0 and 1.4 mg/ℓ, respectively, for the bluegill, Lepomis macrochirus, exposed to tetraethyl lead. The toxicity tests were performed at 20°C with nominal concentrations prepared from carbon filtered Philadelphia tapwater.

Dawson et al. (1977) investigated the toxicity of tetramethyl lead to bluegill and the marine tidewater silverside, Menidia beryllina. Both species were exposed to nominal concentrations of tetramethyl lead in static renewal systems (renewal rate not reported). The 96-hour LC_{50} value of 84 and 13.5 mg/ℓ tetramethyl lead for bluegill and tidewater silversides, respectively, were determined.

The acute toxicity of both tetraethyl lead and tetramethyl lead to plaice, Pleuronectes platessa, was investigated by Maddock and Taylor (1980). The 96-hour flowthrough LC_{50} values of 0.23 and 0.05 mg/ℓ tetraethyl lead and tetramethyl lead, respectively, were determined from measured test concentrations of toxicant in solution.

The elevated toxicity values reported by Turnbull et al. (1954), (48-hour LC_{50} value for bluegill of 1.4 mg/ℓ tetraethyl lead), and Dawson et al. (1977) (96-hour LC_{50} values of 84 and 13.5 mg/ℓ tetramethyl lead for bluegill and tidewater silversides, respectively), are representative of the underestimation of toxicity calculated from nominal

TABLE 6-1

Acute Toxicity of Tetraethyl and Tetramethyl Lead to Fresh and Saltwater Organisms

Species	Duration	Concentration	Method	Effect	Reference
Bluegill *Lepomis macrachirus*	24	2.0 nominal	20°C; static; carbon filtered Philadelphia tap water	LC_{50} tetraethyl lead	Turnbull et al., 1954
	48	1.4 nominal	20°C; static; carbon filtered Philadelphia tap water	LC_{50} tetraethyl lead	Turnbull et al., 1954
	96	84.0 nominal	23°C; static renewal	LC_{50} tetramethyl lead	Dawson et al., 1977
Tidewater silverside *Menidia beryllina*	96	13.5 nominal	20°C; static renewal; marine	LC_{50} tetramethyl lead	Dawson et al., 1977
Plaice *Pleuronectes platessa*	96	0.23 measured	15°C; flowthrough marine	LC_{50} tetraethyl lead	Maddock and Taylor, 1980
	96	0.05 measured	15°C; flowthrough marine	LC_{50} tetramethyl lead	Maddock and Taylor, 1980
Water flea *Daphnia magna*	NR	0.04	NR	Inhibited reproduction	Kolesova and Stroganov, 1973
Common mussel *Mytilus edulis*	96	0.10	14°C; flowthrough marine	LC_{50} tetraethyl lead	Maddock and Taylor, 1980
	96	0.27	14°C; flowthrough marine	LC_{50} tetramethyl lead	Maddock and Taylor, 1980

NR = Not reported

concentrations of toxicant. This may be due to loss of toxins from the test environment by volitalization and degradation.

Maddock and Taylor (1980) also investigated the flowthrough toxicity of tetraethyl lead and tetramethyl lead to a marine molusk, the common mussel, Mytilus edulis. The 96-hour LC_{50} values of 0.10 and 0.27 mg/ℓ for exposure of the common mussel at 14°C were determined for tetraethyl lead and tetramethyl lead, respectively. Kolosova and Stroganov (1973) reported the inhibition of reproduction in the water flea, Daphnia magna, exposed to 0.04 mg/ℓ tetramethyl lead for an unspecified period of time.

Six species of Adriatic fish were exposed to concentrations of tetraethyl lead and tetramethyl lead in water from 0.5-18 mg/ℓ (Giaccio, 1977), and observations of detection and avoidance were reported. There were interspecies differences with respect to the lowest concentration of each toxicant avoided; however, these differences were not related to the type or natural habitat of the fish.

6.2. CHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of lead alkyls to aquatic organisms were not located in the available literature cited in the Appendix.

6.3. PLANT EFFECTS

Marchetti (1978) reported 96-hour EC_{50} values (the concentration necessary to cause a 50% reduction in primary productivity as measured by ^{14}C analysis) of 0.165 and 0.015 tetramethyl lead and tetraethyl lead, respectively, for an algal species, Dunallella tertiolecta. Maddock and Taylor (1980) employed similar techniques to determine the 6-hour EC_{50} values of 1.3 and 0.1 mg/ℓ tetramethyl lead and tetraethyl lead, respectively, for an alga, Phacodactylum tricornutum.

Decreases in cell growth and photosynthetic activity were recorded for a freshwater alga exposed to tetramethyl lead (Silverberg et al., 1977). The 4-hour EC_{50} value of <0.3 mg/ℓ was determined for Ankistrodesmus fulcatus. Cell growth and photosynthetic activity were determined by dry weight/cell counts and ^{14}C-carbonate analysis methods, respectively.

Roederer (1980, 1981b,c, 1983, 1984) described deformations of nuclei, structural alterations of mitochondria and increases in autolytic activity caused by exposure of the unicellular chrysophyte, Poterioochromonas malhamensis, to tetraethyl lead and its derivatives, triethyl lead, diethyl lead and inorganic lead. Tetraethyl and triethyl lead were considerably more toxic than inorganic lead and the resultant ultrastructure alterations were highly complex, generally involving all cell organelles. The most prominent ultrastructure effects of organolead were an increase in the number and/or size of nuclei, contractile vacuoles, chloroplasts and dictyosomes. A marked accumulation of lipid droplets and lysosomes was observed, as was the occurrence of (lipofusin-like) residual bodies. Basal body complexes consisting of up to four basal bodies without visible contacts to the cell membrane or to flagellae were found in the cytoplasm of giant cells.

6.4. RESIDUES

The bioaccumulation potential of tetraethyl lead, (BCF ~18,000 at 0.8 mg/ℓ) in the eastern oyster was found to be potentially dangerous to higher trophic organisms (U.S. EPA, 1979).

Maddock and Taylor (1980) investigated the 96-hour bioaccumulation potential of tetramethyl lead and tetraethyl lead at concentrations up to 0.7 and 0.2 mg/ℓ, respectively, in the shrimp, Crangon crangon, common mussel, Mytilus edulis, and plaice, Pleuronectes platessa. The BCF values of tetramethyl lead and tetraethyl lead for the shrimp, mussel and plaice were 20

and 650, 170 and 120, and 60 and 130, each respectively. The results must be interpreted with caution since, at exposure concentrations in excess of the 96-hour LC_{50} value, a significant proportion of the animals would have died before the end of the test period.

6.5. OTHER RELEVANT INFORMATION

Wong and Chau (1979) investigated the potential for indigenous microorganisms in certain aquatic sediments to methylate organic and inorganic lead compounds to volatile and toxic tetramethyl lead. They reported that methylation of organo-lead compounds occurred readily with and without sediment, but that methylation of inorganic lead was sporadic. Methylation also reportedly increased both the toxicity of lead to several species of freshwater algae and the bioaccumulation of lead to high levels in fish.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Occupational Safety and Health Administration (Code of Federal Regulations, 1981) established a standard of 0.075 mg/m³ for tetraethyl and tetramethyl lead. Potential contribution to the overall exposure by absorption through the skin was also indicated. The ACGIH (1984) recommended a TWA TLV of 0.15 mg/m³ with dermal absorption contributing significantly to the dose for tetraethyl and tetramethyl lead. The ACGIH (1984) recommended a TWA STEL for a 15-minute exposure during an 8-hour workday at 0.5 mg/m³. Guidelines or standards for other lead alkyls were not located in the available literature cited in the Appendix.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of the lead alkyls were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

Data regarding the carcinogenicity of alkyl lead compounds are limited. Robinson (1974, 1976) found a slight increase in skin cancers (7/139) among workers exposed to tetraethyl lead for ≥20 years compared with matched controls (4/139), but this increase was not statistically significant. This study dealt only with current employees and did not include a mortality analysis of workers who left employment due to retirement or illness. Haring (1980) reported preliminary results of a 10-fold increase in multiple myeloma compared to the expected incidence among a group of tetraethyl lead workers, but incidence or additional details were not available. Kantor et al. (1979) suggested an association between development of Wilms' tumor among children and "lead-related" exposure of their fathers, but many influencing factors, including hydrocarbon exposure, precluded a clear conclusion. In mice treated neonatally with tetraethyl lead at 0.6 mg (total dose) in 4 weekly subcutaneous injections and maintained for 49-51 weeks, the incidence of lymphoma, primarily lymphatic leukemia, was 5/41 and 1/26 among treated females and males (Epstein and Mantel, 1968). Lymphomas occurred among 0/48 control females and 1/39 control males. The incidence of hepatomas and fibrosarcomas did not appear to be influenced by tetraethyl lead exposure. The limited mutagenicity data preclude any conclusion regarding human mutagenic potential of alkyl lead compounds. The limited data on any of the alkyl lead compounds are insufficient to draw conclusions regarding the carcinogenic potential of these compounds. As noted in Chapters 4 and 5, tetraalkyl and triaalkyl leads are metabolized to lower alkylated products including inorganic lead; therefore, some of the effects

of inorganic lead may result from exposure to the lead alkyls. Regarding the carcinogenic potential of lead, the U.S. EPA (1984) stated:

> "It is difficult to conclude what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings. However, statistically significant elevations in cancer of the respiratory tract and digestive system in workers exposed to lead and other agents warrant some concern. Since it is clear that lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least that particular lead compound should be regarded as a carcinogen and prudent to treat it as if it were also human carcinogen (as per IARC conclusions and recommendations). However, this statement is qualified by noting that lead has been seen to increase tumorigenesis rates in animals only at relatively high concentrations, and therefore does not seem to be a potent carcinogen. In vitro studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not potent in these systems."

Tetraethyl, tetramethyl and trimethyl lead have not been shown to cause teratogenic malformations among fetuses exposed in utero (see Section 5.3.). Fetotoxic and maternotoxic effects have been reported, each occurring at similar dose levels of alkyl lead. Exposure to tetraethyl lead during pregnancy caused maternotoxicity, fetotoxicity and decreased fertility among rats and mice exposed at 1.0 and 10.0 mg/kg/day on days 6-16 or 5-15, respectively. No apparent toxic effects or decreased reproductive capacity was evident following exposure at 0.01 or 0.10 mg/kg/day in either species (Kennedy et al., 1975). McClain and Becker (1972) reported maternal toxicity, delayed fetal development and increased resorption sites among rats exposed to 15 mg/kg tetraethly lead and 112 mg/kg tetramethyl lead on days 9-11.

Aklyl lead compounds appear to have some effect on reproductive capacity if exposure occurs during early gestation. Kennedy et al. (1975) reported a reduced pregnancy rate among female mice treated at 10 mg/kg tetraethyl lead on days 5-15, with increased resorptions and decreased live fetuses/litter

following treatment at 1.0 and 10.0 mg/kg/day. Similarly, in rats treated at 10.0 mg/kg/day on days 6-18 a low pregnancy rate occurred, and resorptions were increased and live fetuses decreased in groups treated at 1.0 and 10.0 mg/kg/day tetraethyl lead (Kennedy et al., 1975). The number of resorption sites was increased in rats treated at 15 mg/kg/day tetraethyl lead and 112 mg/kg/day tetramethyl lead on days 9-11 of gestation (McClain and Becker, 1972). Odenbro et al. (1982) treated mice with triethyl lead at 3.0 and 6.0 mg/kg on days 3 and 4 of gestation and reported a drop in plasma progesterone and estradiol levels at the time of blastocyst implantation. Decreased levels of these hormones may result in decreased fertility and increased resorption of fetuses. Kihlstrom and Odenbro (1983) reported that triethyl lead at 2.5 mg/kg on day 62 or 63 of gestation to guinea pigs reduced the placental transfer of amino acids to the fetus, which could result in reduced fetal development.

In a 20-week study of tetramethyl and tetraethyl lead administered by gavage, Schepers (1964) reported that rats treated at 0.011 or 0.0017 mg/kg/day (5 days/week), respectively, developed swollen and delicate livers with histological changes (vacuolization and cytoplasmic degeneration) in hepatocytes. Rats treated at 1.08 or 0.17 mg/kg/day, respectively, developed similar but more severe pathologies. Heywood et al. (1979) reported that no signs of toxicity were evident among rhesus monkeys given oral doses at 6 µg/kg/day of tetraethyl or tetramethyl lead for 6 months. Inhalation exposure to tetramethyl and tetraethyl lead at 12 mg/m³ (7 hours/day, 5 days/week) for 150 days caused hepatotoxocity (hepatocyte swelling, nuclear enlargement and vacuolar degeneration) and neural damage among rats. Higher dose levels (22-63 mg/m³) caused a high level of mortality (80-90%) among rats within 5-30 days (Davis et al., 1963).

Increased early mortality occurred among dogs exposed at 4 mg/m³ tetramethyl lead or 12 mg/m³ tetraethyl lead (4 hours/day, 5 days/week).

Exposure to alkyl lead compounds in gasoline through habitual sniffing has led to evidence of impaired heme biosynthesis among children (Boeckx et al. 1977; Robinson, 1978). Among the effects were decreased levels of aminolevulinic acid dehydrogenase, decreased hemoglobin concentrations and increased excretion of aminolevulinic acid in the urine. The effects of inorganic lead on heme synethesis are well documented (U.S. EPA, 1984).

Based on the available toxicological data, it is inappropriate to determine a carcinogenicity risk estimate (q_1^*) for any of the alkyl lead compounds. The toxicity data will, therefore, be used to determine an ADI.

As noted previously, tetraalkyl lead is dealkylated to trialkyl lead which is further dealkylated to lower alkylated products, including inorganic lead. Elevated blood levels of inorganic lead have been associated with lead-induced health effects in humans, including inhibition of heme biosynthesis and neurotoxicity (U.S. EPA, 1984). In adults, the thresholds are <10 µg lead/dℓ blood for impaired heme synthesis and 30-40 µg/dℓ for neurotoxic effects. In children, the thresholds are 10 µg/dℓ for inhibition of heme synthesis and 10-15 µg/dℓ for neurotoxic effects. Exposure to lead alkyls has also been associated with impaired heme biosynthesis (attributable to inorganic lead) and neurotoxicity (attributable to triethyl lead).If an exposure to lead resulting in lead blood levels of 10 µg/dℓ is considered to be a LOAEL, ADIs for lead alkyls can be calculated based on analogy to inorganic lead. The U.S. EPA (1984) has determined, based on several studies, that a slope of 0.06 represents the best estimate for relating blood levels of lead to exposure in drinking water at concentrations <100 µg/ℓ. Therefore, the concentration in water that would result in the threshold blood level of 10 µg/dℓ is 167 µg/ℓ.

Although this concentration is >100 µg/ℓ (the point at which the relationship becomes non-linear), it represents the best estimate. Assuming that an adult consumes 2 ℓ water/day, the LOAEL would be 334 µg/day. Using an uncertainty factor of 100, 10 because the level is a LOAEL and 10 to protect the most sensitive individuals, the ADI for lead would be 3.34 µg/day. This is a very conservative estimate which is developed for purposes of comparison only and is not proposed as an ADI for inorganic lead. The ADIs for the individual lead alkyls can be calculated by multiplying 3.34 µg/day by the ratio of the molecular weight of each lead alkyl (see Table 1-1) to the molecular weight of lead. Thus, for tetraethyl lead, for example:

$$3.34 \text{ µg/day} \times \frac{323.45 \text{ (molecular weight of tetraethyl lead)}}{207.19 \text{ (molecular weight of lead)}} = 5.2 \text{ µg/day}$$

ADIs for the other lead alkyls, similarly calculated, range from 4.08 µg/day for trimethyl lead to 7.02 for tetrabutyl lead.

As mentioned above, the threshold lead blood levels for neurotoxic effects are 30-40 µg/dℓ for adults and 10-15 µg/dℓ for children. Using the slope of 0.06 to relate the blood level to exposure, 10 µg/dℓ is equivalent to 167 µg/ℓ. Assuming a child consumes 1 ℓ water/day, the LOAEL for neurotoxic effects is 167 µg/ℓ. Using an uncertainty factor of 10 because the level is a LOAEL results in an ADI of 16.7 µg/day for lead (this value is estimated for purposes of comparison <u>only</u>, this is <u>not</u> a proposed ADI for inorganic lead). Because children are the most sensitive individuals, an additional uncertainty factor is unnecessary. Using the threshold for adults of 30 µg lead/dℓ blood results in an exposure level of 500 µg/ℓ. Assuming an adult consumes 2 ℓ water/day, the LOAEL for adults is 1000 µg/day. Using an uncertainty factor of 100 (10 for the LOAEL, 10 to protect the most sensitive individuals), the ADI

would be 10 µg/day for lead. On a molar basis, the ADI would be equivalent to 15.6 µg/day for tetraethyl lead and 12.9 µg/day for tetramethyl lead. As stated in U.S. EPA (1984), however, tetraethyl lead and tetramethyl lead "are much more neurotoxic on an equivalent dose basis than inorganic lead". Therefore, it appears to be inappropriate to derive an ADI for lead alkyls leased on analogy to inorganic lead.

Toxicity data for tetraethyl lead and tetramethyl lead in experimental animals can be used to calculate the ADI. Heywood et al. (1979) reported no signs of toxicity following gross and histological examination in rhesus monkeys given oral doses of tetramethyl and tetraethyl lead at 6 µg/kg/day for 6 months. Schepers (1964) reported signs of hepatotoxicity (pancreatic inflammation), cardiac hypertrophy and slight neuronal damage among rats given oral doses at 1.7 µg/kg/day tetraethyl lead or 11.0 µg/kg/day tetramethyl lead on 5 days/week for 20 weeks. Davis et al. (1963) reported hepatic and neural damage among rats exposed to tetraethyl and tetramethyl lead at 12 mg/m³ (equivalent oral dose, 0.80 mg/kg/day, assuming 50% absorption efficiency, 0.223 m³/day breathing rate and 0.35 kg bw for rats) for 7 hours/day, 5 days/week for 150 days. Dogs were more sensitive to the alkyl lead compounds, with decreased survival at 4 mg/m³ tetramethyl lead (equivalent oral dose, 0.04 mg/kg/day, assuming 50% absorption efficiency, 1.5 m³/day breathing rate and 14 kg bw for dogs) or 12 mg/m³ tetraethyl lead (equivalent oral dose, 0.13 mg/kg/day). These data support the conclusion that 1.7 µg/kg/day is a LOAEL for tetraalkyl lead compounds (Schepers, 1964). Since the alkyl lead compounds appear to have similar toxicities and tetraalkyl leads are metabolized to trialkyl forms, this LOAEL will be assumed to be representative of all lead alkyls. The corresponding daily dose based on the animal LOAEL is 1.2 µg/kg/day (1.7

µg/kg/day x 5/7 days). The appropriate uncertainty factor for converting the subchronic animal LOAEL to a chronic human ADI, protective for the most sensitive individuals, is 10,000. The ADI for alkyl lead compounds is, therefore, 0.00012 µg/kg/day or 0.0084 µg/day for a 70 kg man. Until appropriate chronic toxicity data and definitive data on carcinogenicity are available for specific alkyl lead compounds, this ADI of 0.0084 µg/day, determined from toxicity data on tetraethyl lead, is assumed to be sufficiently protective for exposure to alkyl lead compounds in general.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Pertinent toxicity data to derive RQs for lead alkyls are limited to subchronic and teratogenicity studies of tetraethyl and tetramethyl lead (see Sections 5.3. and 5.5.), and are summarized in Table 9-1 (tetraethyl lead) and Table 9-2 (tetramethyl lead).

Heywood et al. (1979) treated rhesus monkeys with oral doses of tetraethyl and tetramethyl lead at 6 µg/kg/day for 6 months with no apparent signs of toxicity or histopathological effects. Since no effects were observed, these data are inappropriate for CS and RQ determination since an RV_e value cannot be established based on no effects.

Kennedy et al. (1975) treated pregnant rats and mice with tetraethyl lead at 0.01,0.10,1.0 or 10.0 mg/kg/day on days 6-16 of gestation (rats) and 5-15 of gestation (mice). At 1.0 and 10.0 mg/kg/day, maternal toxicity, as evidenced by decreased body weight gain, and fetotoxicity were observed in rats and mice. There was no evidence of teratogenicity. The human MEDs associated with 1.0 mg/kg/day in rats and mice are 12.0 and 5.3 mg/day, respectively. The MEDs are calculated by multiplying the dose of 1.0 mg/kg/day by the cube root of the ratio of the animal body weight (0.35 kg for rats, 0.03 kg for mice) to the body weight of a man (70 kg) and by multiplying by 70 kg. The MEDs of 12.0 and 5.3 mg/day correspond to RV_ds of 3.9 and 4.4, respectively. The effect of fetotoxicity, regardless of maternal toxicity and without evidence of teratogenicity, warrants an RV_e of 8. The CSs of 31.2 and 35.2 are obtained by multiplying the respective RV_d by the RV_e. In both cases, the CSs correspond to an RQ of 100 (Table 9-3). McClain and Becker (1972) also found that tetraethyl lead was fetotoxic following oral treatment of pregnant rats with 7.5-30 mg/kg/day on

TABLE 9-1

Toxicity Summary for Tetraethyl Lead

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Purity	Dosage/ Exposure	Dose (mg/kg/day)	Response	Reference
Oral	rat/ COBS	F	20/ group	corn oil	98%	1.0 and 10.0 mg/kg/day on days 6-16 of gestation	1.0 and 10.0	Decreased implantation sites, increased resorptions, decreased number of live fetuses, maternal toxicity	Kennedy et al., 1975
Oral	mouse/ CD-1	F	20/ group	corn oil	98%	1.0 and 10.0 mg/kg/day on days 5-15 of gestation	1.0 and 10.0	Increased resorptions, decreased live fetuses, maternal toxicity	Kennedy et al., 1975
Oral	rat/ Sprague-Dawley	F	3-7/ group	corn oil	"pure"	7.5-30 mg/kg/ day on days 9-11 or 12-14 of gestation	7.5-30	Maternal toxicity, delayed fetal development, increased resorptions	McClain and Becker, 1972
Oral	rat/CD	M,F	6/sex/ group	peanut oil	NR	0.0017 and 0.17 mg/kg/ day, 5 days/ week for 20 weeks	0.0012 and 0.12	Swollen, friable livers, plaques, fatty replacement of thymus, hyperemia and edema of brain and spinal cord, hepatocyte degeneration, neuronal degeneration at both dose levels	Schepers, 1964
Oral	monkey/ rhesus	M,F	2/sex	toluene-ethanol	NR	6 µg/kg/day for 6 months	0.006	None	Heywood et al., 1979
Inhalation	rat/CFN	M,F	5/sex/ group	air/ vapor	NR	12 mg/m³, 7 hours/day, 5 days/week for 150 exposures	1.59	Cerebal control and medullary necrosis, hepatocyte degeneration, necrosis and degeneration of kidney tubules, hemorrhagic lungs	Davis et al., 1963
Inhalation	dog/ beagle	NR	2	air/ vapor	NR	12-42 mg/m³, 7 hours/day, 5 days/week up to 30 exposures	0.27-0.94	All dogs died within 30 exposures	Davis et al., 1963

NR = Not reported

06750

TABLE 9-2

Toxicity Summary for Tetramethyl Lead

Route	Species/ Strain	Sex	No. at Start	Vehicle/ Physical State	Purity	Dosage/ Exposure	Dose (mg/kg/day)	Response	Reference
Oral	rat/ Sprague-Dawley	F	4-8/ group	corn oil	>99%	40-160 mg/kg/ day on days 9-11 or 12-14 of gestation	40-160	Delayed fetal development, maternal toxicity	McClain and Becker, 1972
Oral	rat/CD	M,F	6/sex/ group	peanut oil	NR	0.011 and 1.08 mg/kg/day, 5 days/week for 20 weeks	0.0079 and 0.771	Swollen, friable liver, plaque, fatty replacement of thymus, hyperemia and edema of brain and spinal cord hepatocyte degeneration, neuronal degeneration at both dose levels	Schepers, 1964
Oral	monkey/ rhesus	M,F	2/sex	toluene-ethanol	NR	6 µg/kg/day for 6 months	0.006	None	Heywood et al., 1979
Inhalation	rat/CFN	M,F	5/sex/ group	air/ vapor	NR	12 mg/m³ 7 hours/day, 5 days/week for 150 exposures	1.59	Histopathologic lesions in brain, spinal cord, liver, kidney and lungs; cerebral cortical and medullary necrosis, and degeneration of kidney tubules; hemorrhagic lungs	Davis et al., 1963
Inhalation	dog/ beagle	NR	2	air/ vapor	NR	4mg/m³, 7 hours/day, 5 days/week for 84 and 107 exposures	0.09	Death; dogs exposed to ≥12 mg/m³ died within 15 exposures	Davis et al., 1963

NR - Not reported

08/16/85

06750

TABLE 9-3

Composite Scores for the Toxicity of Tetraethyl Lead

Route	Species	Dose/Exposure	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	rat	1.0 mg/kg/day on days 6-16 of gestation	12.0	3.9	Decreased implantation sites, increased resorptions, decreased number of live fetuses, maternal toxicity	8	31.2	100	Kennedy et al., 1975
Oral	mouse	1.0 mg/kg/day on days 5-15 of gestation	5.3	4.4	Increased resorptions, decreased live fetuses, maternal toxicity	8	35.2	100	Kennedy et al., 1975
Oral	rat	0.0012 mg/kg/day for 20 weeks	0.0014*	9.8	Swollen, friable livers with hepatocyte degeneration; hyperemia and edema of brain and spinal cord with neuronal degeneration	6	58.8	10	Schepers, 1964
Oral	human	0.167 mg/day	0.167	6.7	Inhibition of heme biosynthesis	3	20.1	1000	U.S. EPA, 1984; Boeckx et al., 1977
Inhalation	rat	1.59 mg/kg/day for 150 exposures	1.9*	5.1	Cerebral cortical and medullory necrosis, degeneration of kidney tubules, hepatocyte degeneration, hemorrhagic lungs	6	30.6	100	Davis et al., 1963
Inhalation	dog	0.27 mg/kg/day up to 30 days	.1.1*	5.4	100% mortality	10	54	10	Davis et al., 1963
Inhalation	human	0.73 mg/day	0.73	5.7	Inhibition of heme biosynthesis	3	17.1	1000	U.S. EPA, 1984; Boeckx et al., 1977

*The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

08/16/85

days 9-11 or 12-14 of gestation; however, calculation of a CS for tetraethyl lead for this study is unnecessary, since similar effects were observed in rats at lower doses by Kennedy et al. (1975). McClain and Becker (1972) also treated pregnant rats orally with tetramethyl lead during gestation and observed fetotoxic effects (see Table 9-2) at doses $\geq$40 mg/kg/day. The MED, calculated as described above, is 479 mg/day and corresponds to an RV_d of 1.5 (Table 9-4). The RV_e for fetotoxicity is 8, the CS is 12 and the RQ is 1000.

Schepers (1964) administered tetraethyl lead at 0.17 and 0.0017 mg/kg and tetramethyl lead at 1.08 and 0.011 mg/kg by gavage in peanut oil on 5 days/week for 20 weeks to groups of 12 CD rats each. Rats treated at both dose levels of tetraethyl lead developed swollen, friable livers with histological changes (vacuolization and cytoplasmic degeneration), thymic lesions and neural damage in the brain and spinal cord (hyperemia and edema with neural degeneration, deformity and neuronophagia). Similar toxic effects in the liver and brain occurred in rats given tetramethyl lead at both dose levels. Based on the low dose of tetraethyl lead (0.0017 mg/kg) and tetramethyl lead (0.011 mg/kg) administered on 5 days/week, daily doses are 0.0012 and 0.0079 mg/kg/day, respectively. The corresponding human MED is determined by dividing by an uncertainty factor of 10 to convert from subchronic to chronic exposure and multiplying by the cube root of the body weight ratio (0.35 kg for rat, 70 kg for human) and by 70 kg. The MED would be 0.0014 mg/day tetraethyl lead or 0.0094 mg/day tetramethyl lead for a 70 kg man. The corresponding RV_ds would be 9.8 and 8.5, respectively. The RV_e for gross and histological changes in the liver and neural damage observed among rats exposed to both tetraalkyl lead compounds is 6. The CS for tetraethyl lead is 58.8; for tetramethyl lead, 51. In each case the appropriate RQ value is 10 (see Tables 9-3 and 9-4).

TABLE 9-4

Composite Scores for the Toxicity of Tetramethyl Lead

Route	Species	Dose/Exposure	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	rat	40 mg/kg/day on days 9-11 or 12-14 of gestation	479	1.5	Delayed fetal development, maternal toxicity	8	12	1000	McClain and Becker, 1972
Oral	rat	0.0079 mg/kg/day for 20 weeks	0.0094*	8.5	Swollen, friable liver with hepatocyte degeneration, hyperemia and edema of brain and neuronal degeneration	6	51	10	Schepers, 1964
Oral	human	0.167 mg/day	0.167	6.7	Inhibition of heme biosynthesis	3	20.1	1000	U.S. EPA, 1984; Boeckx et al., 1977
Inhalation	rat	1.59 mg/kg/day for 150 exposures	1.9*	5.1	Cerebral cortical and medullary degeneration, degeneration of kidney tubules, hepatocyte degeneration, hemorrhagic lungs	6	30.6	100	Davis et al., 1963
Inhalation	dog	0.09 mg/kg/day for 84 or 107 exposures	0.37*	6.1	Death	10	61	10	Davis et al., 1963
Inhalation	human	0.73 mg/day	0.73	5.7	Inhibition of heme biosynthesis	3	17.1	1000	U.S. EPA, 1984; Boeckx et al., 1977

*The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

The inhalation study by Davis et al. (1963) on tetraethyl and tetramethyl lead provides sufficient data for determination of CS and RQ values. Rats (CFN strain) were exposed to each compound at 12 mg/m³ (7 hours/day, 5 days/week) for 150 exposures. Death due to infection occurred among 4 of 5 male rats exposed to tetramethyl lead at 12 mg/m³, but deaths were not regarded as exposure-related. Histopathological examinations revealed lesions in the brain and spinal cord, liver, kidney and lungs of rats exposed to both compounds. Lesions included necrosis and degeneration in the brain; hepatocyte degeneration; convoluted tubule and collecting tubule necrosis; and degeneration, edema and hemorrhagic lesions in the lungs. An equivalent animal dosage of 1.59 mg/kg/day is calculated by expanding the exposure of 12 mg/m³ over a 24-hour day and a 7-day week, multiplying by the rat breathing rate of 0.223 m³/day, and dividing by the rat body weight of 0.35 kg. Absorption is assumed to be 100%. Multiplying the rat dose of 1.59 mg/kg/day by the cube root of the body weight ratio and by 70 kg and dividing by an uncertainty factor of 10 to approximate chronic exposure results in a human MED of 1.9 mg/day. The RV_d value based on this MED is 5.1 and the toxic effects warrent an RV_e of 6. The resulting CS and RQ are 30.6 and 100, respectively, and are applicable to both tetraethyl and tetramethyl lead (see Tables 9-3 and 9-4).

Davis et al. (1963) also tested the toxicity of inhaled tetraethyl and tetramethyl lead on Beagle dogs. Dogs appeared to be much more sensitive to the alkyl lead compounds than rats, with mortality occurring among animals exposed at 12 mg/m³ tetraethyl lead and 4 mg/m³ tetramethyl lead. The animal doses (mg/kg/day) are 0.27 and 0.09 mg/kg/day, respectively. The animal doses were obtained by expanding the exposure levels over a 24-hour day and a 7-day week, by multiplying by the dog inhalation rate of 1.5 m³/day (Hertzberg and Dourson, 1983) and by dividing by the average weight

The inhalation study by Davis et al. (1963) on tetraethyl and tetramethyl lead provides sufficient data for determination of CS and RQ values. Rats (CFN strain) were exposed to each compound at 12 mg/m³ (7 hours/day, 5 days/week) for 150 exposures. Death due to infection occurred among 4 of 5 male rats exposed to tetramethyl lead at 12 mg/m³, but deaths were not regarded as exposure-related. Histopathological examinations revealed lesions in the brain and spinal cord, liver, kidney and lungs of rats exposed to both compounds. Lesions included necrosis and degeneration in the brain; hepatocyte degeneration; convoluted tubule and collecting tubule necrosis; and degeneration, edema and hemorrhagic lesions in the lungs. An equivalent animal dosage of 1.59 mg/kg/day is calculated by expanding the exposure of 12 mg/m³ over a 24-hour day and a 7-day week, multiplying by the rat breathing rate of 0.223 m³/day, and dividing by the rat body weight of 0.35 kg. Absorption is assumed to be 100%. Multiplying the rat dose of 1.59 mg/kg/day by the cube root of the body weight ratio and by 70 kg and dividing by an uncertainty factor of 10 to approximate chronic exposure results in a human MED of 1.9 mg/day. The RV_d value based on this MED is 5.1 and the toxic effects warrent an RV_e of 6. The resulting CS and RQ are 30.6 and 100, respectively, and are applicable to both tetraethyl and tetramethyl lead (see Tables 9-3 and 9-4).

Davis et al. (1963) also tested the toxicity of inhaled tetraethyl and tetramethyl lead on Beagle dogs. Dogs appeared to be much more sensitive to the alkyl lead compounds than rats, with mortality occurring among animals exposed at 12 mg/m³ tetraethyl lead and 4 mg/m³ tetramethyl lead. The animal doses (mg/kg/day) are 0.27 and 0.09 mg/kg/day, respectively. The animal doses were obtained by expanding the exposure levels over a 24-hour day and a 7-day week, by multiplying by the dog inhalation rate of 1.5 m³/day (Hertzberg and Dourson, 1983) and by dividing by the average weight

of a dog (14 kg). Absorption was assumed to be 100%. The human MEDs of 1.1 and 0.37 mg/day, respectively, were obtained by multiplying the dog dosages by the cube root of the body weight ratio and by 70 kg, and by dividing by an uncertainty factor of 10 to approximate chronic exposure. The RV_ds for the human MEDs are 5.4 and 6.1 for tetraethyl and tetramethyl lead, respectively. The appropriate RV_e for death is 10; therefore, the CS values for tetraethyl and tetramethyl lead based on these toxicity data in dogs would be 54 and 61, respectively. Based on the CS values, assigned RQ values would be 10 for tetraethyl and tetramethyl lead (see Tables 9-3 and 9-4).

An alternate approach to the derivation of the RQ for lead alkyls would be to use MEDs derived from blood levels of inorganic lead that are associated with toxic effects in humans. This approach may be justified because, as noted in Chapters 4, 5 and 8, lead alkyls are metabolized to lower alkylated products and inorganic lead. One effect of inorganic lead is inhibition of heme biosynthesis (U.S. EPA 1984). Evidence of inhibition of heme biosynthesis (reduced activity of aminolevulinic acid dehydrogenase and increased urinary excretion of aminolevulinic acid) has been observed in children who habitually sniff gasoline (Boeckx et al., 1977), and the effects are attributable to inorganic lead. The threshold blood concentrations of inorganic lead associated with inhibition of heme biosynthesis are <10 mg/dl for adults and 10 µg/dl for children (U.S. EPA, 1984). The U.S. EPA (1984) has determined that blood levels of inorganic lead can be related to exposure to lead in drinking water by a factor of 0.06. Thus, 10 µg lead/dl blood ÷ 0.06 = 167 µg lead/l water. Assuming that an adult consumes 2 l of water/day and a child consumes 1 l of water/day, the concentration in water is equivalent to doses of 0.334 mg/day for adults and 0.167 mg/day for children. The RV_ds are 6.2 and 6.7, respectively.

An appropriate RV_e for this effect would be 2 or 3. Using the more conservative RV_e of 3, CSs would be 18.6 and 20.1, respectively, corresponding to an RQ of 1000. The U.S. EPA (1984) has also determined that blood levels of lead can be related to airborne concentrations of lead by a factor of 1.64 for adults and 1.92 for children. Thus, 10 µg lead/dℓ blood ÷ 1.64 = 6.1 µg/m³ for adults and 10 µg/dℓ ÷ 1.92 = 5.2 µg/m³ for children. Assuming continuous exposure and 100% absorption, 6.1 µg/m³ x 20 m³/day = 122 µg/day (0.122 mg/day), where 20 m³ is the average adult human daily inhalation rate. For a 10-year old child, an inhalation rate can be approximated by the following expression: $0.63\ (38\ kg)^{0.83}$ = 14 m³/day, assuming that a 10-year-old child weighs 38 kg (Snyder et al., 1981). Multiplying the exposure for children of 5.2 µg/m³ by 14 m³/day results in an MED of 72.8 µg/day or 0.73 mg/day, which is equivalent to an RV_d of 5.7. Using an RV_e of 3 results in a CS of 17.1, corresponding to an RQ of 1000.

Exposure of humans to lead alkyls has also been associated with neurotoxic effects; however, the neurotoxicity is attributable to trialkyl lead rather than inorganic lead. Since trialkyl lead is much more neurotoxic than inorganic lead on an equivalent dose basis (U.S. EPA, 1984), it is not appropriate to derive a CS for the neurotoxic effects of lead alkyls based on blood levels of inorganic lead.

The toxicity data and CS and RQ values determined from the study by Davis et al. (1963) are selected as the most appropriate for the ranking of chronic toxicity of the alkyl lead compounds. The dog appears to be the most sensitive species tested. A CS of 54 was determined for tetraethyl lead, while 61 was determined from toxicity data for tetramethyl lead. In both cases, the appropriate RQ value is 10 (Tables 9-5 and 9-6). The CS and

TABLE 9-5

Tetraethyl lead

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	1.10 mg/day
Effect:	mortality
Reference:	Davis et al., 1963
RV_d:	5.4
RV_e:	10
Composite Score:	54
RQ:	10

*Equivalent human dose

TABLE 9-6

Tetramethyl lead

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	0.37 mg/day
Effect:	mortality
Reference:	Davis et al., 1963
RV_d:	6.1
RV_e:	10
Composite Score:	61
RQ:	10

*Equivalent human dose

RQ values determined for rats in the oral toxicity study by Schepers (1964) are almost identical to these values, but have lower human MED values and less severe effects. Based on the lack of toxicity data on other specific alkyl lead compounds and limited evidence that other alkyl leads would have similar toxicities, the RQ value of 10 is appropriate for the ranking of chronic toxicity of other alkyl lead compounds. Additional chronic toxicity data are required to better evaluate specific alkyl lead compounds.

In a previous determination of the RQ for tetraethyl lead (U.S. EPA, 1983), the study of Schepers (1964) was chosen as the most appropriate study because the highest CS was obtained from these data. Although the inhalation study of Davis et al. (1963) was also considered in the previous document, the CS in that determination was not as high as the CS obtained in the present determination. The difference is due to different methods of calculating the MED. In the determination by U.S. EPA (1983), MEDs were calculated by multiplying the inhalation exposure by the human breathing rate of 20 m^3/day and by an absorption coefficient of 0.5, and by dividing by the human body weight. Since the resultant dose was the equivalent human dose, it was not necessary to multiply by the cube root of the body weight ratio. In the current methodology, inhalation exposures are converted to equivalent animal doses by multiplying by the animal breathing rate. The equivalent animal doses must be corrected for interspecies extrapolation by the cube root of the ratio of the animal body weight to the human body weight.

Other differences between the present RQ determination an the U.S. EPA (1983) determination include the use of the higher RV_e of 6 for the effects in the rat studies of Schepers (1964) and Davis et al. (1963), rather than the RV_e of 5 used by U.S. EPA (1983), and the calculation of CSs for the teratogenicity studies of Kennedy et al. (1975) and McClain and

Becker (1972) and for the effects on heme biosynthesis resulting from *in vivo* transformation of lead alkyls to inorganic lead (U.S. EPA, 1984).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The limited data pertinent to the carcinogenicity of alkyl lead compounds are insufficient to show a positive carcinogenic risk. Epstein and Mantel (1968) reported that female mice treated with tetraethyl lead (subcutaneous injection) as neonates and subsequently maintained without treatment for 51 weeks developed lymphoma (5/41), while none occurred among controls (0/48) and treated males showed no increase (Table 9-7). In humans, exposure to tetraethyl lead was associated with a slight but non-significant increase in skin cancers (7/139 vs. 4/139 in matched controls) (Robinson, 1974, 1976). Mutagenicity tests have provided equivocal results (positive results in *Drosophila* and for SCE in human lymphocytes *in vitro*; negative in Ames' assay and mouse dominant lethal assay).

As discussed in Chapters 4 and 5, tetraalkyl and trialkyl leads are metabolized to lower alkylated products, including inorganic lead; therefore, some of the effects of inorganic lead may result from exposure to the lead alkyls. Regarding the carcinogenic potential of lead, the U.S. EPA (1984) stated:

> "It is difficult to conclude what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings. However, statistically significant elevations in cancer of the respiratory tract and digestive system in workers exposed to lead and other agents warrant some concern. Since it is clear that lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least that particular lead compound should be regarded as a carcinogen and prudent to treat it as if it were also human carcinogen (as per IARC conclusions and recommendations). However, this statement is qualified by noting that lead has been seen to increase tumorigenesis rates in animals only at relatively high concentrations, and therefore does not seem to be a potent carcinogen. *In vitro* studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not potent in these systems."

TABLE 9-7

Carcinogenicity Testing of Tetraethyl Lead*

Exposure Route	Species/ Strain	Sex	Dose	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Subcutaneous	mice/Swiss ICR/Ha	F	0.6 mg total dose	21 days	51 weeks	NR	tricaprylin	lymphoreticular system	lymphoma	5/41
		M								1/26
		F	0.0 mg			vehicle only				0/48
		M								1/39

QUALITY OF EVIDENCE

Strengths of Study: Male and female mice were tested. Appropriate control group was included.

Weakness of Study: A non-natural route of administration was used. Treatment was given to neonates over a short duration.

Overall Adequacy: Inadequate

*Source: Epstein and Mantel, 1968

NR = Not reported

Using the IARC criteria for the weight of evidence of carcinogenicity, data on alkyl lead compounds are considered inadequate. Thus, the alkyl lead compounds are tentatively classified as group 3 chemicals. This classification may change if new information on the alkyl lead compounds becomes available. According to the proposed CAG guidelines for carcinogenic risk, alkyl leads would fall in group D, not classified (U.S. EPA, 1984b).

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983-1984.

Ahlberg, J., C. Ramel and C.A. Wachtmeister. 1972. Organolead compounds shown to be genetically active. Ambio. 1: 29-31. (Cited in Grandjean and Andersen, 1982)

Akai, K., K. Yamada, S. Uchigasaki, et al. 1982. Structural alterations of nerve cell in experimental acute tetraethyllead poisoning on rats. Kyorin Igakkai Zasshi. 13(3): 303-313.

Arai, F., Y. Yamamura and M. Yoshida. 1981. Excretion of triethyl lead, diethyl lead and inorganic lead after injection of tetraethyl lead in rabbits. Jap. J. Ind. Health. 23(5): 496-504.

Arai, F., Y. Yamamura, H. Yamauchi and M. Yoshida. 1983. Biliary excretion of diethyllead after injection of tetraethyllead in rabbits. Sangyo Igaku. 25: 175-180.

Boeckx, R.L., B. Posti and F.J. Coodin. 1977. Gasoline sniffing and tetraethyl lead poisoning in children. Pediatrics. 60: 140-145.

Bolanowska, W. 1968. Distribution and excretion of triethyl lead in rats. Br. J. Ind. Med. 25(3): 203-208.

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983-1984.

Ahlberg, J., C. Ramel and C.A. Wachtmeister. 1972. Organolead compounds shown to be genetically active. Ambio. 1: 29-31. (Cited in Grandjean and Andersen, 1982)

Akai, K., K. Yamada, S. Uchigasaki, et al. 1982. Structural alterations of nerve cell in experimental acute tetraethyllead poisoning on rats. Kyorin Igakkai Zasshi. 13(3): 303-313.

Arai, F., Y. Yamamura and M. Yoshida. 1981. Excretion of triethyl lead, diethyl lead and inorganic lead after injection of tetraethyl lead in rabbits. Jap. J. Ind. Health. 23(5): 496-504.

Arai, F., Y. Yamamura, H. Yamauchi and M. Yoshida. 1983. Biliary excretion of diethyllead after injection of tetraethyllead in rabbits. Sangyo Igaku. 25: 175-180.

Boeckx, R.L., B. Posti and F.J. Coodin. 1977. Gasoline sniffing and tetraethyl lead poisoning in children. Pediatrics. 60: 140-145.

Bolanowska, W. 1968. Distribution and excretion of triethyl lead in rats. Br. J. Ind. Med. 25(3): 203-208.

Bolanowska, W. and J.M. Wisniewska-Knypl. 1971. Dealkylation of tetraethyl lead in the homogenates of rat and rabbit tissues. Biochem. Pharmacol. 20(8): 2108-2110.

Bolanowska, W., J. Piotrowski and H. Gorzynski. 1967. Triethyl lead in the biological material in cases of acute tetraethyl lead poisoning. Arch. Toxikol. 22: 278-281. (Cited in Grandjean and Nielsen, 1979)

Booze, R.M., C.F. Mactutus, Z. Annau and H.A. Tilson. 1983. Neonatal triethyl lead neurotoxicity in rat pups: Initial behavioral observations and quantification. Neurobehav. Toxicol. Teratol. 5(3): 367-376.

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Atmospheric Science Center. SRI International, Menlo Park, CA. Contract 68-02-3452. 198 p.

Brown, S.L., F.Y. Chan, J.L. Jones, D.H. Liu and K.E. McCaleb. 1975a. Research program on hazard priority ranking of manufactured chemicals (Chemicals 1-20). Stanford Research Institute, Menlo Park, CA. 191 p. NTIS PB-263 161.

Byington, K.H., D.A. Yates and W.A. Mullens. 1980. Binding of triethyl lead chloride by hemoglobin. Toxicol. Appl. Pharmacol. 52: 379-385.

Cassells, D.A.K. and E.C. Dodds. 1946. Tetra-ethyl lead poisoing. Br. Med. J. 2: 681-685. (Cited in Grandjean and Nielsen, 1979)

Chand, P. and J. Clausen. 1982. Triethyl lead toxicity in relation to brain glutathione and glutathione S-transferase. Toxicol. Lett. 12: 181-184.

Chang, L.W., P.R. Wade, K.R. Reuhl and M.J. Olson. 1980. Ultrastructural changes in renal proximal tubules after tetraethyllead intoxication. Environ. Res. 23(1): 208-223.

Charlou, J.L., M.P. Caprais, G. Blanchard and G. Martin. 1982. Degradation of TEL [tetraethyllead] in seawater. Environ. Technol. Lett. 3(9): 415-424.

Chau, Y.K. and P.T.S. Wong. 1980. Biotransformation and toxicity of lead in the aquatic environment. Lead Mar. Environ. Proc. Int. Experts Discuss. M. Branica and Z. Konrad, Ed. Meeting Date 1977, 225-31. Pergamon, Oxford, England.

Chau, Y. K., P.T.S. Wong, G.A. Bengert and O. Kramar. 1979. Determination of tetraalkyllead compounds in water, sediment and fish samples. Analyt. Chem. 51: 186-188.

Chau, Y.K., P.T.S. Wong, O. Kramar, et al. 1980. Occurrence of tetraalkyl lead compounds in the aquatic environment. Bull. Environ. Contam. Toxicol. 24: 265-269.

Chau, Y.K., P.T.S. Wong, G.A. Bengert and J.L. Dunn. 1984. Determination of dialkylead, trialkylead and lead (I) compounds in sediment and biological samples. Anal. Chem. 56: 271-274.

CMR (Chemical Marketing Reporter). 1982. Chemical Profile - Lead Alkyls. Chemical Marketing Reporter, Feb. 1, 1982.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. U.S. Department of Labor, OSHA, Washington, DC. 29 CFR 1910.

Coulehan, J.L., W. Hirsch, J. Brillman, et al. 1983. Gasoline sniffing and lead toxicity in Navajo adolescents. Pediatrics. 71: 113-117.

Cragg, B. and S. Rees. 1984. Increased body:brain weight ratio in developing rats after low exposure to organic lead. Exp. Neurol. 86(1): 113-121.

Cremer, J.E. 1959. Biochemical studies on the toxicity of tetraethyl lead and other organolead compounds. Br. J. Ind. Med. 16: 191-199.

Cremer, J.E. and S. Callaway. 1961. Further studies on the toxicity of some tetra and trialkyl lead compounds. Br. J. Ind. Med. 18: 277-282.

Cupitt, L.T. 1980. Fate of toxic and hazardous materials in the air environment. U.S. EPA, ESRL, Research Triangle Park, NC. EPA-600/S3-80-084.

Davis, R.K., A.W. Horton, E.E. Larson and A.L. Stemmer. 1963. Inhalation of tetramethyl lead and tetraethyl lead. Arch. Environ. Health. 6: 473-479.

Dawson, G.W., A.L. Jennings, D. Drozdowski and E. Rider. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazard. Mater. 1: 303-318.

CMR (Chemical Marketing Reporter). 1982. Chemical Profile - Lead Alkyls. Chemical Marketing Reporter, Feb. 1, 1982.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. U.S. Department of Labor, OSHA, Washington, DC. 29 CFR 1910.

Coulehan, J.L., W. Hirsch, J. Brillman, et al. 1983. Gasoline sniffing and lead toxicity in Navajo adolescents. Pediatrics. 71: 113-117.

Cragg, B. and S. Rees. 1984. Increased body:brain weight ratio in developing rats after low exposure to organic lead. Exp. Neurol. 86(1): 113-121.

Cremer, J.E. 1959. Biochemical studies on the toxicity of tetraethyl lead and other organolead compounds. Br. J. Ind. Med. 16: 191-199.

Cremer, J.E. and S. Callaway. 1961. Further studies on the toxicity of some tetra and trialkyl lead compounds. Br. J. Ind. Med. 18: 277-282.

Cupitt, L.T. 1980. Fate of toxic and hazardous materials in the air environment. U.S. EPA, ESRL, Research Triangle Park, NC. EPA-600/S3-80-084.

Davis, R.K., A.W. Horton, E.E. Larson and A.L. Stemmer. 1963. Inhalation of tetramethyl lead and tetraethyl lead. Arch. Environ. Health. 6: 473-479.

Dawson, G.W., A.L. Jennings, D. Drozdowski and E. Rider. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazard. Mater. 1: 303-318.

DeJonghe, W.R.A., D. Chakraborti and F.C. Adams. 1981. Identification and determination of individual tetraalkyllead species in air. Environ. Sci. Tecnnol. 15: 1217-1222.

Diehl, K.H., A. Rosopulo, W. Kreuzer and G.K. Judel. 1983. Behavior of tetraalkyl leads in the soil and their uptake by plants. Z. Pflanzenernaehr. Bodenkd. 146(5): 551-559.

Dumas, J.P., L. Pazdernik, S. Belloncik, D. Bouchard and G. Vaillancourt. 1977. Methylation of lead in aquatic medium. Water Pollut. Res. Can. 12: 91-100.

Edwards, H.W. and R.J. Rosenvold. 1974. Uptake of tetraethyl lead vapor by atmospheric dust components. Trace Contam. Environ. 2: 59-63.

Epstein, S.S. and N. Mantel. 1968. Carcinogenicity of tetraethyllead. Experientia. 24(6): 580-581.

Feldhake, C.J. and C.D. Stevens. 1963. The solubility of tetraethyl lead in water. J. Chem. Eng. Data. 8: 196-197.

Ferreira da Silva, D., U. Schroeder and H. Diehl. 1983. Metabolism of tetraorganolead compounds by rat liver microsomal monooxygenase. II. Enzymic dealkylation of tetraethyllead. Xenobiotica. 13(10): 583-590.

Ferris, N.J. and B.G. Cragg. 1984. Organic lead and histological parameters of brain development. Acta Neuropathol. 63: 306-312.

Giaccio, M. 1977. The behavior of some ichthyologic species of the Adriatic in the presence of tetramethyl and tetraethyl lead. Quad. Merceol. 16(1): 55-62.

Grandjean, P. and O. Andersen. 1982. Toxicity of lead additives [letter]. Lancet. 2: 333-334.

Grandjean, P. and T. Nielsen. 1979. Organolead compounds: Environmental health aspects. Residue Rev. 97-148.

Gruber, G.I. 1975. Assessment of industrial hazardous waste practices, organic chemicals, pesticides and explosives industries. Office of Solid Waste Management Programs, U.S. EPA, Washington, DC. p. 5-46 to 5-49. EPA-68-01-2919. NTIS PB 251307.

Haring, M. 1980. Mortality and industrial hygiene study of workers exposed to tetraethyl lead. In: Directory of Ongoing Research in Cancer Epidemiology 1980, C.S. Muir and G. Wagner, Ed. IARC, Lyon, France. p. 428. (Cited in Grandjean and Andersen, 1982)

Harrison, R.M. and D.P.H. Laxen. 1977. Organolead compounds adsorbed upon atmospheric particulates: A minor component of urban air. Atmos. Environ. 11(2): 201-203. (CA 87:89739q)

Harrison, R.M. and D.P.H. Laxen. 1978a. Sink proceses for tetraalkylated compounds in the atmosphere. Environ. Sci. Technol. 12: 13384-13392.

Harrison, R.M. and D.P.H. Laxen. 1978b. Natural source of tetraalkyl lead in air. Nature. 275: 738-740.

Harrison, R.M., R. Perry and R.A. Wellings. 1975. Lead and cadmium in precipitation: Their contribution to pollution. J. Air Pollut. Control Assoc. 25: 627-630.

Hawley, G.G. 1977. The Condensed Chemical Dictionary, 9th ed. Van Nostrand Reinhold Co., New York. p. 847, 850-1.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1: 3-142.

Hayakawa, K. 1972. Microdetermination and dynamic aspects of in vivo alkyl lead compounds. II. Dynamic aspects of alkyl lead compounds in vivo. Nippon Eiseigaku Zasshi. 26(6): 526-535.

Heard, M.J., A.C. Wells, D. Newton and A.C. Chamberlain. 1979. Human uptake and metabolism of tetraethyl and tetramethyl lead vapor labeled with lead-203. Manage. Control Heavy Met. Environ., Int. Conf. p. 103-108.

Hertzberg, R.C. and M.L. Dourson. 1983. Health Risk from Less Than Lifetime Toxicant Exposure. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH. (Draft)

Heywood, R., R.W. James and R.J. Sortwell. 1978. The intravenous toxicity of tetraalkyl lead compounds in rhesus monkeys. Toxicol. Lett. 2(4): 187-197.

Heywood, R., R.W. James, A.H. Pulsford, et al. 1979. Chronic oral administration of alkyl lead solutions to the rhesus monkey. Toxicol. Lett. 4(2): 119-125.

IARC (International Agency for Research on Cancer). 1980. Some Metals and Metallic Compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Vol. 23, p. 325-415.

Jarvie, A.W.P., R.N. Markall and H.R. Potter. 1975. Chemical alkylation of lead. Nature. 255: 217-218.

Jarvie, A.W.P., R.N. Markall and H.R. Potter. 1981. Decomposition of organolead compounds in aqueous systems. Environ. Res. 25(2): 241-249.

Kantor, A.F., M.G. Curnen, J.W. McC Meigs and J.T. Flannery. 1979. Occupations of fathers of patients with Wilms's tumour. J. Epidemiol. Community Health. 33: 253-256. (Cited in IARC, 1980)

Karkos, J. and J. Sikora. 1973. Neuropathological changes during experimental poisoning with ethyl gasoline. Neuropatol. Pol. 11(1): 99-108. (CA 79:49605)

Kawamori, M., K. Matsumoto and T. Matsui. 1983. Acute intoxication by tetraethyllead. I. Toxic symptoms of the central nervous system and spontaneous motor activity. Kyorin Kgakkai Zasshi. 14: 3-11.

Kehoe, R.A. and F. Thamann. 1931. The behavior of lead in the animal organism. II. Tetraethyl lead. Am. J. Hyg. 13: 478-498.

Kenaga, E.E. and C.A.I. Goring. 1978. Relationship between water solubility, soil-sorption, octanol-water partitioning, and bioconcentration of chemicals in biota. Prepublication copy of paper dated October 13, 1978, given at the 3rd Aquatic Toxicology Symp., American Society for Testing and Materials, New Orleans, LA, October 17-18.

Kennedy, G.L. and D.W. Arnold. 1971. Absence of mutagenic effects after treatment of mice with lead compounds. Environ. Mutagen. Soc. Newsl. 5: 37. (Cited in IARC, 1980)

Kennedy, G.L., D.W. Arnold and J.C. Calandra. 1975. Teratogenic evaluation of lead compounds in mice and rats. Food Cosmet. Toxicol. 13(6): 629-632.

Kihlstrom, I and A. Odenbro. 1983. Effect of triethyl lead on the placental uptake and transfer of the nonmetabolizable alpha-aminoisobutyric acid in guinea pigs. Toxicology. 27(2): 111-118.

Kolosova, L.V. and M.S. Stroganov. 1973. Analysis of the mechanism of action of some pesticides on Daphnia according to biological indexes. Eksp. Vodn. Toksikol. 5: 134-145.

Konat, G. and J. Clausen. 1976. Triethyllead-induced hypomyelination in the developing rat forebrain. Exp. Neurol. 50(1): 124-133.

Konat, G. and J. Clausen. 1978. Protein composition of forebrain myelin isolated from triethyl lead-intoxicated young rats. J. Neurochem. 30(4): 907-909.

Konat, G., H. Offner and J. Clausen. 1976. Triethyl lead-restrained myelin deposition and protein synthesis in the developing rat forebrain. Exp. Neurol. 52(1): 58-65.

Konat, G. H. Offner and J. Clausen. 1979. The effect of triethyl lead on total and myelin protein synthesis in the rat forebrain slices. J. Neurochem. 32(1): 187-190.

Korenev, V.S. 1970. Characteristics of the initial phases of chronic poisoning with tetraethyl lead. Nauch. Tr., Irkutsk. Gos. Med. Inst. 98: 116-21. (CA 78:38859)

Lane, J.C. 1980. Gasoline and other motor fuels. In: Kirk-Othmer Encyclopedia of Chemical Technology, Volume 11, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 671.

Laug, E.P. and F.M. Kunze. 1948. The penetration of lead through the skin. J. Ind. Hyg. Toxicol. 30: 265-259.

Lazrus, A.L., E. Lorange and J.P. Lodge, Jr. 1970. Lead and other metal ions in United States precipitation. Environ. Sci. Technol. 4: 55-58.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co., NY. p. 15-16.

Maddock, B.G. and D. Taylor. 1980. The acute toxicity and bioaccumulation of some lead alkyl compounds in marine animals. In: Lead in the Marine Environment, M. Branica and Z. Konrad, Ed. Pergamon, Oxford, UK. p. 233-262.

Malpass, D.B., L.W. Fannin and J.J. Ligi. 1981. Organometallics, δ-bonded alkyls and aryls. In: Kirk-Othmer Encyclopedia of Chemical Technology, Volume 16, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 579-583.

Marchetti, R. 1978. Acute toxicity of alkyl leads to some marine organisms. Mar. Pollut. Bull. 9(8): 206-207.

Matsui, T., K. Matsumoto and M. Kawamori. 1984. Acute intoxication by tetraethyl lead. II. Effects on the operant behavior in rats. Kyorin Igakkai Zasshi. 14(2): 129-135. (CA 100:186825)

McClain, R.M. and B.A. Becker. 1972. Effects of organolead compounds on rat embryonic and fetal development. Toxicol. Appl. Pharmacol. 21(2): 265-274.

Morgan, A. and A. Holmes. 1978. The fate of lead in petrol-engine exhaust particulates inhaled by the rat. Environ. Res. 15(1): 44-56.

Mortensen, R.A. 1942. The absorption of lead tetraethyl with radioactive lead as indicator. J. Ind. Hyg. Toxicol. 24: 285-288.

Nielsen, O.J., T. Nielsen and P. Pagsberg. 1982. Direct spectrokinetic investigation of the reactivity of hydroxyl radical with tetraalkyl lead compounds in gas phase. Estimate of lifetimes of tetraalkyl lead compounds in ambient air. Energy Res. Abstr. 8(18): 17.

Niklowitz, W.J. 1974. Ultrastructural effects of acute tetraethyl lead poisoning on nerve cells of the rabbit brain. Environ. Res. 8(1): 17-36.

Odenbro, A., J. Orberg and E. Lundqvist. 1982. Progesterone and oestrogen concentrations in plasma during blastocyst implantation in mice exposed to triethyl lead. Acta. Pharmacol. Toxicol. (Copenhagan). 50: 241-245.

Potter, H.R., A.W.P. Jarvie and R.N. Markall. 1977. Detection and determination of alkyl lead compounds in natural waters. Water Pollut. Control. 76(1): 123-128.

Prough, R.A., M.A. Stalmach, P. Wiebkin and J.W. Bridges. 1981. The microsomal metabolism of the organometallic derivatives of the Group-IV elements, germanium, tin and lead. Biochem. J. 196(3): 763-770.

Przybylowski, J., W. Matuszewski, A. Podolecki and K. Kaminski. 1977. Blood serum and tissue monoamine oxidase and tissue glyoxalase I. Activities in experimental chronic intoxication with gasoline and lead gasoline. Bromatol. Chem. Toksykol. 10(1): 75-78. (CA 87:48654)

Rabenstein, D.L., S.J. Backs and A.A. Isab. 1981. NMR studies of the complexation of trimethyl lead by glutathione in aqueous solution in intact human erythrocytes. J. Am. Chem. Soc. 103(10): 2836-2841.

Radziuk, B., Y. Thomassen, J.C. Vanloon and Y.K. Chau. 1979. Determination of alkyl lead compounds in air by gas chromatography and atomic adsorption spectrometry. Anal. Chim. Acta. 105: 255-262.

Robinson, J.W. and I.A.L. Rhodes. 1980. Solubility of TEL in seawater. The effect of suspended particles. J. Environ. Sci. Health. A. 15: 201-209.

Robinson, R.O. 1978. Tetraethyl lead poisoning from gasoline sniffing. J. Am. Med. Assoc. 240: 1373-1374.

Robinson, T.R. 1974. 20-Year mortality of tetraethyl lead workers. J. Occup. Med. 16: 601-605.

Robinson, T.R. 1976. The health of long service tetraethyl lead workers. J. Occup. Med. 18: 31-40.

Roederer, G. 1980. On the toxic effects of tetraethyl lead and its derivatives on the chrysophyte Poterioochromonas malhamensis. I. Tetraethyl lead. Environ. Res. 23(2): 371-384.

Roederer, G. 1981a. Fate and toxicity of tetraalkyl lead and its derivatives in aquatic environments. Heavy Met. Environ., Int. Conf., 3rd. 250-253.

Roederer, G. 1981b. On the toxic effects of tetraethyl lead and its derivatives on the chrysophyte Poterioochromonas malhamensis. II. Triethyl lead, diethyl lead, and inorganic lead. Environ. Res. 25(2): 361-371.

Roederer, G. 1981c. Inhibition of mitosis and formation of polyploid nuclei in poterioochromonas malhamensis by triethyl lead. Eur. J. Cell. Biol. 24: 340.

Roederer, G. 1982. On the toxic effects of tetraethyl lead and its derivatives on the chrysophyte Poterioochromonas malhamensis. III. Chemical analyses. J. Environ. Sci. Health, Part A. A17(1): 1-20.

Roederer, G. 1983. Trimethyllead toxicity in the freshwater algae Euglena gracilis and Poterioochromonas malhamensis. Heavy Met. Environ. Int. Conf. 1: 362-365.

Roederer, G. 1984. On the toxic effects of tetrethyllead and its derivatives on the chrysophyte Poterioochromonas malhamensis. V. Electron microscopical studies. Environ. Exp. Bot. 24(1): 17-30.

Ross, CA. 1982. Gasoline sniffing and lead encephalopathy. Can. Med. Assoc. J. 127: 1195-1197.

Schepers, G.W.H. 1964. Tetraethyl lead and tetramethyl lead. Arch. Environ. Health. 8: 277-295.

Schmidt, U. and F. Huber. 1976. Methylation of organolead and lead (II) compounds to $(CH_3)_4Pb$ by micro-organisms. Nature. 259: 157-158.

Schroeder, T., D.D. Avery and H.A. Cross. 1972a. LD_{50} value of tetraethyl lead. Experientia. 28(4): 425-426.

Schroeder, T., D.D. Avery and H.A. Cross. 1972b. Tetraethyl lead dose response curve for mortality in laboratory rats. Experientia. 28(8): 923-924.

Shapiro, H. and F.W. Frey. 1967. Lead compounds (organic). In: Kirk-Othmer Encyclopedia of Chemical Technology, Volume 12, 2nd ed., A. Standen, Ed. John Wiley and Sons, Inc., NY. p. 282-299.

Silverberg, B.A., P.T.S. Wong and Y.K. Chau. 1977. Effect of tetramethyl lead on freshwater green algae. Arch. Environ. Contam. Toxicol. 5(3): 305-313.

Sirota, G.R. and J.F. Uthe. 1977. Determination of tetraalkyllead compounds in biological materials. Analyt. Chem. 49: 823-825.

Snyder, W.S., M.J. Cook, E.S. Nasset, L.R. Karhausen, G.P. Harvells and I.H. Tipton. 1981. Rep. Task Group on Reference Man. Int. Commission on Radiological Protection No. 23. Pergammon Press, Oxford, England. p. 480.

SRI (Stanford Research Institute). 1984. 1984 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA. p. 671.

Thompson, J.A.J. 1981. Production of lead alkyls in marine sediments. Heavy Met. Environ., Int. Conf., 3rd. p. 653-656.

Tiravanti, G. and G. Boari. 1979. Potential pollution of a marine environment by lead alkyls: The cavtat incident. Environ. Sci. Technol. 13: 849-854.

Turnbull, H., J.G. DeMann and R.F. Weston. 1954. Toxicity of various refinery materials to freshwater fish. Ind. Eng. Chem. 46(2): 324-333.

U.S. EPA. 1977. Computer printout of non-confidential production data from TSCA Inventory. U.S. EPA, OPTS, CID, Washington, DC.

U.S. EPA. 1979. Status Report 8EHQ-1078-0249.

U.S. EPA. 1984a. Air Quality Criteria for Lead. 2nd External Review. Environmental Criteria and Assessment Office, U.S. EPA, Research Triangle Park, NC. EPA 600/8-83-A28A.

U.S. EPA. 1984b. Proposed Guidelines for Carcinogen Risk Assessment. Fed. Reg. 49(22): 46294-46299.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. USITC Publ. 1422. U.S. International Trade Commission, Washington, DC.

USITC (U.S. International Trade Commission). 1984. Synthetic Organic Chemicals. U.S. Production and Sales, 1983. USITC Publ. 1588. U.S. International Trade Commission, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY. p. 1085-1091.

Weber, R.C., P.A. Parker and M. Bowser. 1981. Vapor pressure distribution of selected organic chemicals. U.S. EPA, Cincinnati, OH. 39 p. EPA 600/2-81-021.

Wong, P.T.S. and Y.K. Chau. 1979. Methylation and toxicity of lead in the aquatic environment. Manage. Control Heavy Met. Environ., Int. Conf. p. 131-134.

Wong, P.T.S., Y.K. Chau and P.L. Luxon. 1975. Methylation of lead in the environment. Nature. 253: 263-264.

Wong, P.T.S., Y.K. Chau, O. Kramar and G.A. Bengert. 1981. Accumulation and depuration of tetramethyl lead by rainbow trout. Water Res. 15(5): 621-625.

Yamamura, Y., J. Takakura, F. Hirayama, H. Yamauchi and M. Yoshida. 1975. Tetraethyl lead poisoning caused by cleaning work in the aviation fuel tank. Jap. J. Ind. Health. 17: 223-235. (Cited in U.S. EPA, 1984a)

Yamamura, Y., F. Arai, M. Yoshida and E. Shimada. 1979. Comparison of lead clearance rate in the rabbit after intravenous injection of tetraethyl lead and inorganic lead salts. Sei Marianna Ika Daigaku Zasshi. 7(1): 10-20. (Cited from CA 93:20314)

Yamamura, Y., H. Yamauchi and F. Arai. 1981. Urinary excretion pattern of triethyl lead, diethyl lead and inorganic lead in tetraethyllead poisoning. Ind. Health. 19(2): 125-132.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in February and March, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, the following document was reviewed for pertinent data:

U.S. EPA. 1980. Ambient Water Quality Criteria for Lead. U.S. EPA, Office of Water Regulations and Standards. Washington, DC. EPA 440/5-80-057. NTIS, PB81-117681.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. U.S. EPA, Office Pesticide Programs, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.